Research Article

Efficacy and Safety of Pidotimod in SARS-CoV-2 Management: A Real-world Evidence Study

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ABSTRACT

Background: The role of pidotimod in immune stimulation in conditions like asthma, chronic obstructive pulmonary disease, and recurrent respiratory tract infections is well established. This has led to its exploration in COVID-19, which is also characterized by immune dysregulation. We determined the efficacy and safety of pidotimod in paucisymptomatic SARS-CoV-2 patients.

Methods: In this retrospective study, the Electronic Medical Records (EMRs) of paucisymptomatic SARS-CoV-2 patients visiting the outpatient department at Kunal Institute of Medical Specialities Pvt. Ltd., Bashir Bagh, Hyderabad, India between March 2021 and July 2021 were reviewed. Patients having mild/moderate symptoms with PCR-documented SARS-CoV-2 positive from a nasopharyngeal sample were included in the study and divided into two groups (3:2): Group A (n=77) included patients who received pidotimod along with the standard of care treatment, and Group B (n=50) received only standard of care treatment for 14 days. The effectiveness outcomes were the number of days taken for fever resolution, for relief of other symptoms, and negative swab test. Change in levels of various biomarkers involved in the pathogenesis of COVID-19 from baseline to 7 days and 14 days of treatment, was observed. Safety was assessed by adverse events reported during the treatment period.

Results: Overall, 140 patients were included, of which 13 were excluded as they had signs of pneumonia or respiratory failure. The mean age of the patients was 32.88 ± 10.86 and 31.20 ± 11.81 years in Group A and Group B respectively. Co-morbidities such as diabetes (28.6% in Group A and 24% in Group B) and hypertension (32.5% in Group A and 28% in Group B) were observed in the patients. The majority of the patients presented with fever and cough. Patients in Group A showed an earlier fever resolution (3.58 ± 1.04 days *vs.* 7.29 ± 3.12 days) as well as earlier resolution of other symptoms (4.16 days ± 1.03 days *vs.* 7.10 days ± 2.45 days), when compared to Group B, respectively. Similarly, the swab test of patients was reported negative earlier (10.56 days ± 3.11 days) in Group A *vs.* Group B (13.74 days ± 2.45 days). Furthermore, a significant decline ($p<0.001$) in elevated levels of various biomarkers like CRP (64.27% *vs.* 59.52%) and IL-6 (51.03% *vs.* 33.31%) was observed after 14 days in patients receiving pidotimod, when compared with control group. A noteworthy improvement in the levels of d-dimer (521.48 ng/ml ± 166.14 ng/ml to 377.74 ng/ml ± 102.59 ng/ml) was observed in the pidotimod group after 7 days of treatment than that in the control group (656.58 ng/ml ± 193.93 ng/ml to 529.74 ng/ml ± 156.47 ng/ml); with corresponding reductions of 27.56% and 19.31%, respectively. Similarly, a significant reduction ($p<0.001$) in the levels of ferritin was found in the pidotimod group (45.66%) as compared to the control group (30.39%). No serious adverse events were reported during the 14 days of treatment in both groups.

Conclusion: Pidotimod, as an adjuvant therapy for the treatment of paucisymptomatic SARS-CoV-2 patients, was observed to decrease the levels of inflammatory mediators and other biological markers in patients. Pidotimod appears to have a potential role in managing SARS-CoV-2 patients.

Keywords: Paucisymptomatic; SARS-CoV-2; COVID-19; Immunomodulator; Pidotimod, Biomarkers;

Introduction

The coronavirus disease 2019 (COVID-19) was first reported in Wuhan (People's Republic of China) in early December 2019 and later spread worldwide [1]. It was declared as a pandemic by the World Health Organization (WHO) on 11 March, 2020 [2]. The etiological agent was designated as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The virus has been suggested to "have a zoonotic origin from animal", and like other respiratory pathogens, it also spreads through air borne transmission with coughing and sneezing [3].

After encountering the respiratory mucosa,

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SARS-CoV-2 ingresses the host cells *via* the angiotensin-converting enzyme-2 (ACE-2) receptor. Subsequently, the virus transcribes its Ribonucleic Acid (RNA) and produces structural as well as non-structural proteins; especially N-protein that blocks the Interferon (IFN) production. It results in interruption of host cell signaling, because of which the virus replicates itself and easily invades several cells without being noticed by the host body. Therefore, the host may remain asymptomatic in the initial days of the infection. The onset of the initial symptoms is followed by either eradication of the virus by the immune system ensuing the patient's betterment or the advancement of the virus into the lungs, fostering damage to the endothelium and oxidative stress. This leads to an overactivation of the inflammatory response, initiated by Interleukin (IL)-6 that activates macrophages, monocytes, and T-cells, causing a "cytokine storm" [4]. Concisely, along with the total viral load and the adaptive immune response, the role of the innate immune system in consequence of SARS-CoV-2 infection is imperative.

The most common COVID-19 clinical presentation (approximately 80% of the patients) is a mild disease with or without pneumonia. Only 20%-30% of patients require hospitalization, while most of them are home-managed [5]. Infected patients may present with any of the symptoms, including fever, high temperature (>37.3°C), cough, myalgia, sputum production, headache, hemoptysis, diarrhea, dyspnea and in some cases, Acute Respiratory Distress Syndrome (ARDS), acute cardiac injury or secondary infection [6,7]. These subjective clinical symptoms can be elucidated by using biological markers (biomarkers) as they provide objective values throughout the progression of the disease. Hence, categorizing patients into mild, severe or critical becomes more discrete, enabling early interventions [8].

Studies have revealed the role of various biomarkers in the disease pathogenesis of COVID-19 and how their altered levels are allied with the severity of the disease. The elevated levels of biomarkers like d-dimer, lactate dehydrogenase, C-Reactive Protein (CRP), Interleukin-6 (IL-6), cardiac troponin, renal markers (serum urea, creatinine and markers of glomerular filtration rate), and decreased level of platelets are reported to be associated with COVID-19 [9].

The host immune response to viremia causes various symptoms, lung injury, and elevated levels of plasma pro-inflammatory mediators. Drugs rebalancing the host immune system (immunomodulators) may be useful to prevent the clinical worsening of SARS-CoV-2 infection [10]. Immunomodulators, such as pidotimod, have been used both in children and in adults to prevent exacerbations in patients affected by obstructive lung diseases [11]. As a synthetic dipeptide molecule (3-l-pyro-glutamyl-l-thiazolidine-4carboxilic acid) with immunomodulatory activity, pidotimod focuses on both innate and adaptive immune responses [12]. The well-established role of pidotimod in immune stimulation in conditions like asthma, COPD, and recurrent respiratory tract infections, has led to its exploration in COVID-19, which is characterized by immune dysregulation [11].

However, there is a paucity of evidence-based studies in real-world settings regarding pidotimod's role in COVID-19 patients. This study aimed to evaluate the efficacy and safety of pidotimod in paucisymptomatic COVID-19 patients.

Methods

■ Patients and study design

This single-centre retrospective observational study was conducted at Kunal Institute of Medical Specialities Pvt. Ltd., Bashir Bagh, Hyderabad, India. The retrospectively collected data included the patient's electronic medical records (EMR) visiting the outpatient department between March 2021- July 2021. Adult patients having mild/moderate symptoms with PCR-documented SARS-CoV-2 positive from a nasopharyngeal sample were included in the study [13].

■ Treatment plan

The SARS-CoV-2 positive paucisymptomatic patients included in the study were divided into two groups. Group A received the standard of care treatment following the institutional protocol in combination with pidotimod 800 mg (twice daily), and Group B received only standard of care treatment. The standard of care treatment included doxycycline 100 mg (twice

daily for five days), ivermectin 12 mg (twice daily for three days), favipiravir 1800 mg (twice daily on day 1 followed by 800 mg twice daily for 13 days), methylprednisolone 16 mg (twice daily for five days, then tapered), apixaban 2.5 mg (twice daily for 15 days), vitamin C 500 mg (twice daily for 15 days), zinc acetate 50 mg (once daily for 15 days), and vitamin D 60000 units (once a week for eight weeks).

Study Outcomes

All demographic, epidemiological, clinical and laboratory findings were collected at baseline and at 7 and 14-days of treatment. The effectiveness outcomes were measured in terms of the number of days taken for fever resolution, for relief from other symptoms and for negative swab test report. Furthermore, laboratory findings were evaluated to determine the decrease in elevated levels of various biomarkers including complete blood count, d-dimer, CRP, ferritin, and IL6. Safety was also determined in terms of reported Adverse Events (AEs) during the treatment period (14 days).

Statistical Analysis

Data analyses were done using Microsoft Excel (2016) and R studio 3.5.3. Descriptive statistics was exhibited in the form of categorical and continuous variables. Categorical variables (like gender) were expressed as percentages and compared by using Chi-square/Fisher exact test. In contrast, continuous variables (like age and scores) were expressed as mean and SD and compared by using appropriate tests. The normality was assessed prior to all the continuous variables. Independent Sample T-Test, and Non-Normal Data, Mann Whitney U-Test were used to find the significant difference between the groups. Statistical significance was considered at $p<0.05$.

Ethical Statement

Patient's confidentiality was maintained using anonymized and de-identified data at the source level. The study approval and data collection was performed as per the ethical standards (Declaration of the Helsinki in 1964). The study was conducted after taking approval from the institutional ethical committee.

Results

Baseline characteristics

Out of a total of 140 patients, 13 were excluded as they had signs of pneumonia and acute respiratory failure; Group A had 77 and Group B had 50 patients. The mean age of the patients was 32.88 years ± 10.86 years and 31.20 years ± 11.81 years in Group A and Group B respectively. Co-morbidities such as diabetes (28.6% in Group A and 24% in Group B) and hypertension (32.5% in Group A and 28% in Group B) were observed in the patients. The majority of the patients presented with fever and cough. Baseline demographic/clinical characteristics of the patients included in the study are outlined in Table 1. The mean time to onset of symptoms in Group A was 3.64 days ± 1.62 days, while in group B it was found to be 3.00 days ± 1.01 days.

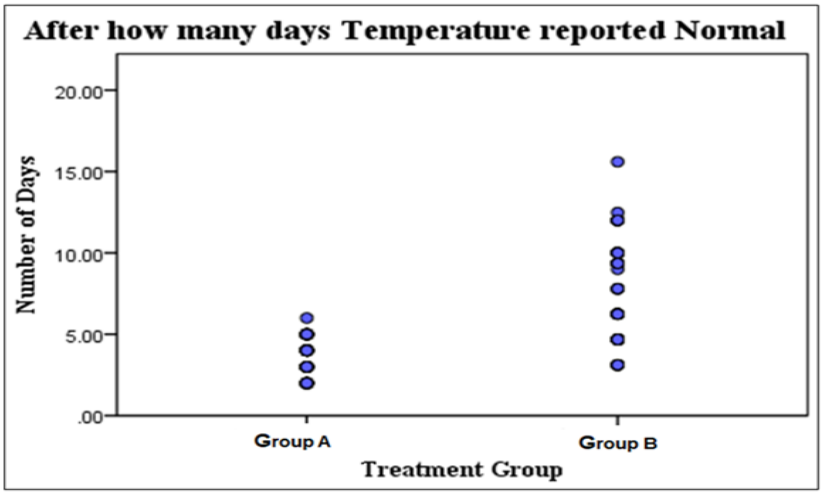

Figure 1: Fever resolution graph of Group A (pidotimod group) vs. Group B (control group).

However, patients included in the study did not show any radiographic signs of pneumonia. Laboratory findings revealed that all patients had evidence of hyper-inflammation, including three readings of temperature>98.6°F, elevated levels of pro-inflammatory mediators like d-dimer, LDH, blood urea, CRP, ferritin, AST and IL6. No considerable differences in symptom severity, laboratory and clinical features were found between both the groups (Table 1).

Table 1: Baseline characteristics of patients included in the study

Parameters		GROUP A (Routine Treatment + Pidotimod) N=77	GROUP B (Routine Treatment) N=50
Age (Years)	**N (%)**	**77 (60.6%)**	**50 (39.4%)**
	Mean ± SD	**32.88 ± 10.86**	**31.20 ± 11.81**
Gender			
Male		22 (28.6%)	28 (56%)
Female		52 (67.5%)	22 (44%)
Unknown		3 (3.9%)	0 (0%)
History of Direct Exposure			
Not Available		4 (5.2%)	2 (4%)
Yes		73 (94.8%)	48 (96%)
Time-to-Symptom's onset (Days)	**N (%)**	77 (100%)	50 (100%)
	Mean ± SD	**3.64 ± 1.62**	**3.00 ± 1.01**
Symptoms			
Fever		77 (100%)	50 (100%)
Cough		56 (73%)	35 (70%)
Dry cough		12 (15.6%)	4 (8%)
Chills		1 (1.3%)	2 (4%)
Cold		0 (0%)	4 (8%)
Myalgia		14 (18.2%)	9 (18%)
Nausea		1 (1.3%)	0 (0%)
Sore Throat		7 (9.1%)	2 (4%)
Diarrhea		4 (5.2%)	1 (2%)
Body aches		13 (16.9%)	10 (20%)
Headache		11 (14.3%)	9 (18%)
Loss of Smell		19 (24.7%)	13 (26%)
Loss of Taste		19 (24.7%)	10 (20%)
Loss of Appetite		3 (3.9%)	1 (2%)
Shortness of Breath (SOB)		10 (13%)	2 (4%)
Anosmia		5 (6.5%)	3 (6%)
Anorexia		6 (7.8%)	0 (0%)
Weakness		15 (19.5%)	1 (2%)
Rhinitis		0 (0%)	2 (4%)
Co-morbidities			
Diabetes Mellitus		22 (28.6%)	12 (24%)
Hypertension		25 (32.5%)	14 (28%)
Coronary Artery Disease (CAD)		9 (11.7%)	0 (0%)
Hypothyroid		2 (2.6%)	0 (0%)
Dyslipidemia		1 (1.3%)	0 (0%)
Obstructive Sleep Apnea (OSA)		3 (3.9%)	0 (0%)
COPD History		7 (9.1%)	3 (6%)
Smoking		0 (0%)	3 (6%)
Obesity		3 (3.9%)	0 (0%)
Asthma		3 (3.9%)	0 (0%)

Study Outcomes

Efficacy

Patients in Group A showed an earlier fever resolution (3.58 days ± 1.04 days) than Group B (7.29 days ± 3.12 days) **(Figure 1)**. The number of days in which other symptoms were relieved after initiation of the treatment was also less in Group A (4.16 days ± 1.03 days) than in Group B (7.10 days ± 2.45 days). Similarly, in Group A, swab test of the patients was reported negative earlier (10.56 days ± 3.11 days) when compared with Group B (13.74 days ± 2.45 days).

Following the treatment, a significant decline in levels of inflammatory mediators was found in Group A, when compared to Group B. The CRP levels were higher than the normal range in all the patients before initiating the treatment. CRP levels significantly improved ($p<0.001$) in Group A (from 10.47 71 mg/dL ± 6.4171 mg/dL to 5.38 71 mg/dL ± 2.71 mg/dL after 7 days and to 3.74 71 mg/dL ± 1.47 mg/dL after 14 days) as compared to Group B (from 12.3371 mg/dL ± 4.20 71 mg/dL to 9.78 71 mg/dL ± 3.36 mg/dL after 7 days and to 4.99 71 mg/dL ± 1.71 mg/dL after 14 days), with the corresponding reductions of 64.27% and 59.52%, respectively after 14 days **(Figure 2a)**. The elevated levels of IL-6, a predictor marker for disease severity of COVID-19, was also significantly reduced ($p<0.001$) in Group A (from 24.73 pg/ml ± 9.49 pg/ml to 12.11 pg/ml ± 5.80 pg/ml) in comparison to Group B (from 28.52 pg/ml ± 13.26 pg/ml to 19.02 pg/ml ± 8.84 pg/ml) after 14 days. Corresponding reductions of 51.03% and 33.31% were observed in Group A and Group B, respectively **(Figure 2b)**. Further, abnormal coagulation function included elevated d-dimer levels, which has been reported to be involved in the disease progression of COVID-19. In corollary, the baseline values of d-dimer in the patients were found to be more than 500 ng/ml. However, after the treatment of pidotimod, a considerable decline was observed in the values of d-dimer (from 521.48 ng/ml ± 166.14 ng/ml to 377.74 ng/ml ± 102.59 ng/ml) in Group A after 7 days of treatment as compared to Group B (from 656.58 ng/ml ± 193.93 ng/ml to 529.74 ng/ml ± 156.47 ng/ml); with corresponding reductions of 27.56% and 19.31%, respectively **(Figure 2c)**. Ferritin is a key mediator of immune dysregulation, contributing to the cytokine storm, which is often associated with fatal outcomes. A significant improvement ($p<0.001$) in ferritin levels after 7 days of treatment was found in Group A (from 490.81 ± 173.47 to 265.66 ± 108.13 ng/ml) as compared to Group B (400.42 ± 125.38 to 278.70 ± 92.45 ng/ml) with a reduction of 45.66% and 30.39%, respectively **(Figure 2d)**.

Safety

The common adverse events observed in Group

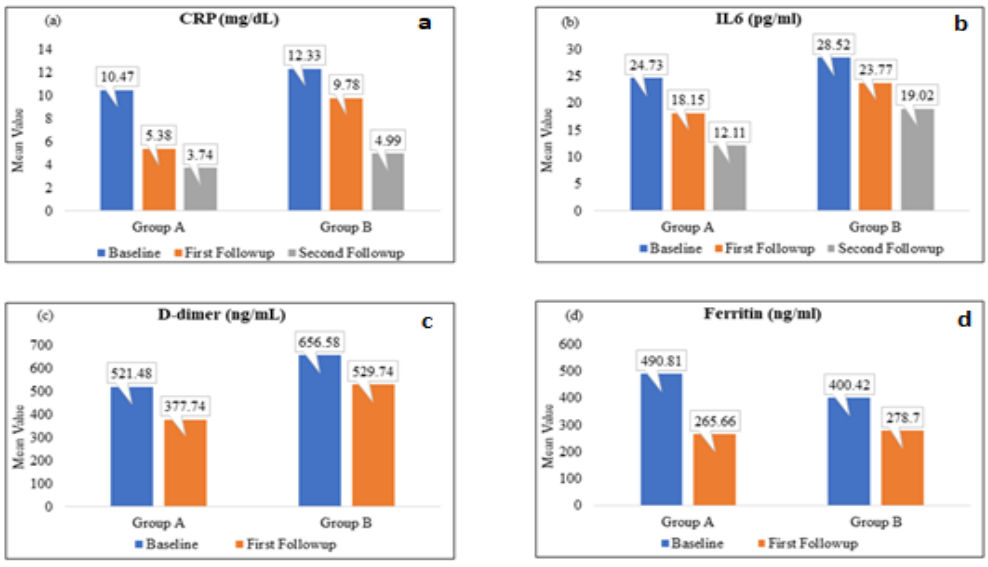

Figure 2: (a) Changes in CRP at first and second follow-up from baseline; (b) Changes in IL-6 levels at first and second follow-up from baseline; (c) Changes in d-dimer levels at first follow-up from baseline; (d) Changes in ferritin levels at first follow-up from baseline in Group A (pidotimod group) and Group B (control group).

A were nausea (6.49%), headache (5.19%) and lethargy (5.19%), while in Group B, nausea (12%), headache (10%), myalgia (8%) and arthralgia (8%) were generally reported. However, no major drug-induced adverse events or worsening of disease during the treatment regimen were reported in both groups, indicating good tolerability and safety profiles of both treatments.

Discussion

This retrospective study has reported that the use of pidotimod as an adjuvant therapy to standard of care regimen in patients with paucisymptomatic COVID-19. Pidotimod showed earlier resolution of symptoms and a significant reduction in proinflammatory mediators in positive mild/moderate cases of COVID-19 in comparison to the standard of care regimen alone.

The host immune response to SARS-CoV-2 plays an important role in disease pathogenesis and clinical manifestations. The virus activates and produces unrestricted inflammatory responses; and in case of severe infection, immune abnormalities may lead to secondary infections, septic shock, and severe multiple organ dysfunction [14]. Further, laboratory biomarkers (serum levels of CRP, d-dimers, ferritin, cardiac troponin and IL-6) depicting the state of hyperinflammation play a crucial role in assessing the disease severity and rational triaging [15]. Therefore, early modulation of the inflammatory state associated with COVID-19 may offer a promising approach to edge the pulmonary complications of the disease, minimize the need for intensive care unit support and eventually mortality [4].

Pidotimod exhibits an immunomodulatory activity by ameliorating both innate and adaptive immune responses. It is reported to promote phagocytosis and chemotaxis; activate neutrophils and enhance the cytotoxic activity of the natural killer cells [16]. Furthermore, it stimulates the activation of the cellular immune processes by promoting lymphocyte proliferation, effectively restoring the ratio of auxiliary and inhibitory T cells, regulating the secretion of γ-interferon and interleukin-2. It also stimulates the proliferation of B lymphocytes and the formation of antibodies against pathogens [17]. Moreover, it has been reported to be associated with the upregulation of a number of genes involved in the activation of innate immune responses and antimicrobial activity [18]. All these elucidated effects of pidotimod shows its potential as a new approach in the management of COVID-19.

The findings of the present study demonstrated a shorter duration of the infection in the pidotimod group in comparison to the control group. These findings are in corollary with the results of studies carried out by other researchers for recurrent respiratory infections. According to the paper of Li, et al. published in 2009, they reported earlier disappearance of fever, pulmonary rale, cough and adenoids in pidotimod treated patients as compared to patients under control treatment along with the shorter duration of RTI and days of antibiotic usage in the former group [19]. Similarly, another group of researchers has stated that pidotimod could alleviate the symptoms of an acute phase of RTI, reduce the dosage of antibiotics, reduce the risk of antibiotic-resistant bacteria, and shorten the course of treatment [20].

The present study is in corollary with the work of other research groups in terms of the response of various drug therapies using different biomarkers. According to the paper of Purwati, et al. which was published in 2020, they observed a significant decrease in the elevated levels of biomarkers such as CRP and IL-6, in all treatment groups (lopinavir/ritonavir-azithromycin, lopinavir/ritonavir-doxycycline, and azithromycin-hydroxychloroquine) than in the control group (standard of care regimen) after 7 days of treatment in patients with mild to moderate COVID-19 infections. However, no significant difference in the improvement of d-dimer levels was found [21]. In a case series, patients whose symptoms improved after sarilumab treatment had a corresponding rapid decrease in CRP levels, neutrophil to lymphocyte ratio and d-dimer levels. It was thus concluded that these biomarkers are potential symbols of response to the treatment [22].

The efficacy and safety of pidotimod in paucisymptomatic COVID-19 positive patients (n=20) with fever and cough without acute respiratory failure or signs of pneumonia were evaluated by Ucciferri, et al. The findings of the study revealed that patients receiving pidotimod showed an earlier clinical resolution of symptoms than the control group (4.10 days ± 2.18 days

vs. 7.50 days ± 2.63 days) in corollary with the findings of the present study [23]. In another case report, two patients who had taken pidotimod showed significant improvement in their clinical symptoms with pneumonia foci disappearing after a few days (detected by CT scan) [24].

In the present study, the adverse events reported in the pidotimod group were observed to be similar to that of the control group, showing that the addition of pidotimod was well tolerated.

Conclusion

The use of pidotimod was found to be associated with a reduction of systemic symptoms of the disease as well as improvement in various biomarker levels in the patients. Pidotimod can be considered as a potential therapeutic approach in COVID-19 but prospective studies with a bigger sample size are warranted to confirm these results.

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