Comparison of IMC-2 alone and IMC-2 and Paxlovid® shows substantial short and long-term efficacy in reducing symptoms of Long COVID with combination therapy: a case series

David Putrino
Icahn School of Medicine at Mount Sinai https://orcid.org/0000-0002-2232-3324
William Pridgen
tsasurgery@gmail.com

1. Tuscaloosa Surgical Associates

Case Report

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Abstract

Introduction

Long COVID (LC), an infection-associated chronic illness (IACI) with no currently approved treatments. In order to address SARS-CoV-2 persistence and herpesvirus reactivation, which have been implicated as drivers of LC, sustained use of antiviral combinations may have utility in treating patients with the illness.

Methods

We studied a convenience sample of patients engaged in an extended course of a combination of antiviral medications, either IMC-2 Only (IO) or IMC-2 with the addition of 15 days of Paxlovid (IP), prescribed off-label, to people with LC being treated at an outpatient clinic. The Patient Global Impression of Change (PGIC) was used to measure response to the therapy over time, with a primary focus on fatigue symptom reporting and a secondary focus on brain fog and dysautonomia symptoms. In addition, visual analogue scales (VAS) were used to track perceived symptom improvements.

Results

Twenty-seven people with LC were approached for treatment, of whom 24 completed one or both protocols. Twelve were treated with IO and twelve were given the continuous IP combination. A reduction in fatigue, reported on the PGIC, was observed in both groups, but those who received IP experienced a statistically significant improvement compared to those who received IO ($p < 0.0001$). Similarly, using a VAS, patients reported an average 55.3% ($p < 0.0001$) greater reduction of fatigue in the IP group, compared with the IO group. Patients who completed the IP intervention demonstrated significant durability in their clinical benefit, with reported symptom improvements remaining consistent at 120-, 305- and 731-day follow-ups.

Discussion

This small, open-label case series provides pilot evidence to support the need for a larger trial of combination antivirals for people living with LC. Based on these results a larger, controlled trial of IMC-2 paired with Paxlovid should be conducted.

Introduction

A subset of individuals infected with SARS-CoV-2 virus develop new symptoms or sequelae that do not resolve for months or years. This condition is known as Long COVID (LC) or or Post-Acute Sequelae of COVID (PASC). Conservative estimates for LC suggest there are at least 65 million people suffering with this condition worldwide, and some sources suggest that this estimate is higher.[1–2] The societal and

financial consequences of untreated LC are have been estimated at almost 3 trillion dollars in the United States alone.[3] There are likely multiple drivers of LC symptoms, but two of the most prominent include persisting reservoirs of SARS-CoV-2 and SARS CoV-2-related downregulation of the immune response, resulting in the reactivation of dormant viruses such as the herpesviruses.[4–5]

To address potential SARS-CoV-2 persistence in LC, multiple monotherapeutic clinical trials of antivirals have been conducted or are underway.[6] More than one 15 and 30-day Paxlovid studies in LC failed to show efficacy, but did support the drug's tolerability and safety and the RECOVER Initiative is currently running a 15- and 25-day Paxlovid study.[7, 8] Remdesivir is presently being studied in Finland, and still others are hoping to show monoclonal antibody efficacy for a LC indication.[9] Another proposed mechanism of action is that a proportion of IACI patients experience significant symptom burden as a result of persistent or reactivating herpesviruses.[10–11] IMC-2 is a novel combination of Valacyclovir and Celecoxib that may have utility in addressing persistent or reactivating herpesviruses and may be relevant to the clinical care of people with Long COVID. Valacyclovir antiviral properties are well established, yet celecoxib also has strong antiviral properties.[12–17] Specifically, gammaherpesviruses and alphaherpesviruses both upregulate using COX-2, and to a lesser degree COX-1 enzymes. Thus celecoxib, at the proper concentration to block both COX-1 and COX-2 enzymes, mean that celecoxib can be used as an effective antiviral complement to valacyclovir. Trials utilizing celecoxib alone were found to have efficacy in treating acute infections with SARS-CoV-2.[18] Similarly, Paxlovid, due to its 3C-like proteases (cysteine), potentially has activity against over a dozen different viruses in addition to SARS-CoV-2.[19–20]

To date, all of the reported antiviral trials attempted for LC have only tested single antiviral agents. However, it is possible that treatment of SARS-CoV-2 persistence might require treatment with synergistic use of agents with different mechanisms of action, or trials that use longer dosing periods of antivirals.[6] The question of whether more can be done by combining antivirals in order to target persistent SARS-CoV-2 infection alongside reactivation of other previously latent viruses is highly relevant and important to innovating on care for people with LC. Thus, the use of a combination like IMC-2 could potentially provide continuous daily suppression of multiple pathogens, thus reversing the viral reactivation of herpes viruses and potentially other viruses.

In the present work, we describe a case series where patients with LC received either IMC-2 only (IO), or IMC-2 combined with a 15-day course of Paxlovid (IP). We compare and contrast outcomes between the two groups and discuss the feasibility of these data to justify a larger placebo-controlled randomized controlled trial.

Methods

All patients seeking care at a LC clinic that were prescribed either the IO and IP medication combinations provided prospective, informed consent for their data to be used for both retrospective review and

quality improvement purposes. Ethics approval for analysis and publication of these data were provided by the IRCM Office for Human Research Protection of HHS (IRB Approval Number: IRCM-2025-446). These data were collected in accordance with the Declaration of Helsinki and the FDA's Good Clinical Practice recommendations. The privacy rights of human subjects were observed, and appropriate clinical oversight was in place.

Participant Inclusion

All patient data presented in this case series came from people who met LC diagnostic criteria per the Centers for Disease Control (CDC) and National Academies of Science Engineering and Medicine (NASEM) clinical case definitions. Patients of all genders, who were over the age of 18 and had been symptomatic with LC for at least 5 months were given the opportunity to contribute data to this case series.

Symptom Rating

All patients rated the severity of three symptoms: fatigue, brain fog and dysautonomia (dizziness and tachycardia) using a five-point Likert scale (none, mild, moderate, moderately severe, severe) at the time of enrollment. Subsequently, percentage improvement of these symptoms as well as a Patient Global Impression of Change (PGIC) at three post-treatment timepoints (120, 305 and 731 days) were also collected. The PGIC was presented as 2 scales: a 7- and a 10-point scale where patients were asked to rate their perceived improvement at each post-treatment timepoint. Possible responses on the 7-point PGIC scale ranged from 1 (No change, or condition has gotten worse) to 7 (A great deal better and a considerable improvement that has made all the difference). The 10-point scale has responses about symptom severity ranging from − 5 (much worse) to 5 (much better), with a central point of "no change" at 0. The PGIC has been well-validated as a patient-reported outcome that can capture meaningful subjective change in chronic symptom severity.[21] Although it has not been specifically validated in LC, it has been well-used and validated in other complex chronic illnesses such as fibromyalgia and was therefore selected as a reasonable endpoint to measure self-reported symptom change in the patient sample.[22] The primary endpoint of this work was the PGIC in fatigue at 120 days post-treatment. We also tracked changes to both PGIC scale data for brain fog and dysautonomia symptoms at 120 days post-protocol, and changes in both PGIC scale data for fatigue, brain fog and dysautonomia symptoms at 305 and 731 days post-protocol as secondary endpoints.

Intervention

This open-label trial of IMC-2 and Paxlovid had two arms with the opportunity for crossover. Patients who consented to off-label use of IMC-2 to treat Long COVID symptoms were given the opportunity to take IMC-2 alone (Arm 1; IO), or to include a 15-day Paxlovid course with their IMC-2 administration (Arm

2; IP). Patients who opted for Arm 1 were given the opportunity to crossover to Arm 2 once they had completed the 120-day Arm 1 protocol.

Statistical Analysis

Between-group comparisons of symptom improvements, VAS, and PGIC data at different timepoints were conducted using unpaired samples t-tests. Within-group comparisons of symptom improvement and PGIC data at different timepoints were conducted using one-way, repeated measures ANOVAs. Statistical adjustment for multiple comparisons in the secondary outcome statistical analyses was performed using Bonferroni Correction. All analyses were performed in MATLAB (Mathworks, Natick, MA).

Results

Patient characteristics

Data presented in this case series were collected from patients with Long COVID attending a single, Alabama-based clinic from April, 2022 to February 2024. In this time period, a total of 27 patients were approached with the opportunity to treat their Long COVID with either the IO or IP therapies. Twenty-four patients (4 male) completed one or both interventional arms. A flow diagram in CONSORT format illustrating patient participation in the different interventional arms is presented as Fig. 1. Initially, twelve patients opted for IO therapy (1 male) and twelve patients (3 male) opted for the IP. In addition, three of the initial patients (1 male) who engaged in IO therapy opted to also attempt the IP combination.

Adverse event and side effect reporting

There were no reported side effects or adverse events for patients who took the IO treatment combination. For those who took the IP treatment combination, some minor side effects were reported (Table 1), most commonly increased fatigue (reported in 40% of patients) and dysgeusia (reported in 86.7% of patients). These minor side effects appeared during the initiation of the 15-day course of Paxlovid, and were noted to resolve soon after the end of the Paxlovid course.

Table 1
Summary of Side Effect Profiles of IO and IP treatment groups.

Side Effect	Percentage reported in IO Group	Percentage reported in IP Group
Body Aches/Discomfort	0	26.6%
Flu-like symptoms	0	13.3%
Depression	0	13.3%
Headaches/Dizziness	0	13.3%
Diarrhea	0	13.3%
Increased Fatigue	0	40%
Bad taste in mouth	0	86.7%

Comparison of IO and IP outcomes after 120 days of treatment

The primary endpoint was to determine if there was a significant change in fatigue when 15 days of Paxlovid is given along with 120 days of valacyclovir and celecoxib when compared to 120 days of valacyclovir and celecoxib alone. On average, patients who completed the IP protocol scored 34.5% higher on their PGIC fatigue rating than people on the IO protocol (Fig. 2; $p < 0.0001$). Additional outcomes between the two groups showed a similar trend of statistically significant improvement on the IP protocol and are listed as Table 2.

Table 2
Differences in 120-day outcomes between the two protocols

Outcome	IO average reported score (± standard deviation)	IP average reported score (± standard deviation)	Percentage difference (%)	p-value
Fatigue (PGIC: 7-point Likert)	4.8 (± 0.63)	6.8 (± 0.4)	IP response is 34.5% greater	**p < 0.0001**
Dysautonomia (PGIC: 7-point Likert)	4.1 (± 2.3)	6.9 (± 0.3)	IP response is 50.9% greater	**p < 0.0001**
Brain Fog (PGIC: 7-point Likert)	4.2 (± 1.7)	6.4 (± 0.7)	IP response is 41.5% greater	**p < 0.0001**
Fatigue (PGIC: 10-point Likert)	2.3 (± 0.9)	4.0 (± 1.3)	IP response is 55.3% greater	**p < 0.0001**
Dysautonomia (PGIC: 10-point Likert)	1.8 (± 3.2)	4.1 (± 1.5)	IP response is 78.0% greater	**p < 0.0001**
Brain Fog (PGIC: 10-point Likert)	2.5 (± 1.3)	3.8 (± 1.5)	IP response is 41.3% greater	**p < 0.0001**

Durability of treatment response in the IP cohort

The durability of each patient's treatment response to the IP intervention was tracked over 600 days beyond the initial 120-day protocol. All 15 participants in the IP group completed all three follow-up timepoints. There were no statistically significant differences in symptom reporting for the primary outcome measure (Fig. 3) or any of the measured symptoms (Table 3) at any of the three timepoints, indicating that treatment responses yielded sustained improvements that lasted up to 600 days beyond the cessation of the combined antiviral protocol.

Table 3
Durability of treatment responses for patients on the IP protocol up to 720 days

Outcome	120-Day Follow-up	305-Day Follow-up	720-Day Follow-up	p-value
Fatigue (PGIC: 7-point Likert)	6.8 (± 0.4)	6.6 (± 0.5)	6.8 (± 0.4)	$p > 0.05$
Dysautonomia (PGIC: 7-point Likert)	6.9 (± 0.3)	6.6 (± 0.7)	6.8 (± 0.4)	$p > 0.05$
Brain Fog (PGIC: 7-point Likert)	6.4 (± 0.7)	6.8 (± 0.4)	6.8 (± 0.6)	$p > 0.05$
Fatigue (PGIC: 10-point Likert)	4.0 (± 1.3)	4.0 (± 1.1)	3.8 (± 1.3)	$p > 0.05$
Dysautonomia (PGIC: 10-point Likert)	4.1 (± 1.5)	4.1 (± 1.2)	4.5 (± 1.1)	$p > 0.05$
Brain Fog (PGIC: 10-point Likert)	3.8 (± 1.5)	4.1 (± 1.4)	4.1 (± 1.4)	$p > 0.05$

Discussion

This initial open-label case series shows that Long COVID patients treated with either IMC-2 or a combination of IMC-2 and Paxlovid report a significant benefit to their Long COVID symptoms, with those who received the combination therapy with Paxlovid, benefiting the most for a prolonged follow-up duration. The benefits reported by these patients were highly durable, with the majority of patients continuing to report benefits in fatigue, dysautonomia and cognitive symptoms over 600 days post-protocol. In addition, the combination therapies were very well-tolerated by the cohort studied, with minimal adverse events reported and no drop-outs for reasons related to side-effects. This is a promising initial feasibility and efficacy trial that highlights the utility of combination antiviral therapies to treat a subset of patients with Long COVID and provides rationale and feasibility for a larger, randomized, double-blind, placebo-controlled trial.

There are various reasons why a combination of Celecoxib, Valacyclovir and Paxlovid are well-positioned as therapies to address symptoms that arise from Long COVID. We know from acute COVID-19 that the

SARS CoV-2 virus can cause a PGE2 storm in a substantial proportion of patients via upregulating cyclooxygenase-2 (COX-2) and downregulating prostaglandin E2 (PGE2)-degrading enzymes within the host cell. As such, treatment with 200 mg twice a day of celecoxib was associated with a lower mortality rate in COVID-19 compared to a control group.[6] Upregulated COX-2 levels can also modulate the events in Epstein Barr Virus life cycle related to latency-lytic reactivation.[12] In addition to the gammaherpesviruses, the alphaherpesviruses also upregulate using COX-2, and to a lesser degree COX-1 enzymes. Therefore, the ability of the celecoxib, at the proper concentration, to block both COX-1 and COX-2 enzymes makes this drug an effective antiviral complement to valacyclovir at combating herpesvirus reactivation.

Paxlovid, a combination of Nirmatrelvir and Ritonavir, has activity against SARS-CoV-2 but also, potentially, against other reactivating viruses. Nirmatrelvir, a protease inhibitor, inhibits viral replication by cleaving viral polyproteins involved in replication. Ritonavir has no activity against SARS-CoV-2, yet its role is to specifically inhibit the metabolism of Nirmatrelvir by CYP3A (cytochrome P450-3A), thus boosting its potency. However, Paxlovid, due to its 3C-like proteases (cysteine), potentially has activity against over a dozen different viruses beyond simply SARS-CoV-2.[19–20]

Both latent pathogen reactivation and viral persistence have been implicated multiple times as potential symptom drivers of Long COVID.[4–6, 23] These drivers can occur in combination or in isolation in different people with Long COVID, but a large proportion of people with Long COVID are likely suffering from severe symptoms as a result of these drivers. Taken together, this provides a strong rationale for why a large number of patients in this case series have responded so positively to this combination of antiviral medications.

Limitations

There are several limitations to the presented work. This was an open-label case series, where both selection bias of patients who were seeking care and the placebo effect may both be factors in the outcomes seen in the analysis. In addition, with the exception of the use of the PGIC and VAS methodology for measuring symptom improvement and severity was not performed using gold-standard symptom measures, but rather subjective symptom rating from the patient population. However, while these limitations should temper the immediate generalizability of these findings, we believe that the outcomes reported in this study by the patient population provide sufficient feasibility and efficacy justification for a larger clinical trial.

Conclusion

There appears to be synergy of IMC-2 and Paxlovid as evidenced by a seeming improved performance of the antiviral combination compared to IMC-2 alone in this pilot study. There are substantial limitations in a single site, open-label retrospective review of data of this type, but we believe that these early results

are sufficiently promising to justify a larger clinical trial. A randomized, double-blind placebo-controlled trial is needed for this therapeutic combination.

Declarations

Conflict of interest

WLP is a partner and founder at PridCor Therapeutics, a company that holds a patent containing components making up IMC-2.

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References

1. Hastie EC, Lowe DJ, McAuley A, Mills NL, Winter AJ, Black C, et al. True Prevalence of long COVID in a nationwide, population cohort study. Nature Communications. Article number:7892(2023)
2. Christina van der Felz-Cornelis, Turk F, Sweetman J, Khunti K, Gabbay M, Shepherd J, et al. Prevalence of mental health conditions and brain fog in people with long COVID: A systematic review and meta-analysis. General Hospital Psychiatry; Volume 88, May–June 2024, Pages 10-22.
3. Cutler DM. The costs of long COVID. In JAMA Health Forum 2022 May 6 (Vol. 3, No. 5, pp.e221809-e221809). American Medical Association.
4. Iwasaki A, Putrino D. Why we need a deeper understanding of the pathophysiology of long COVID. The Lancet Infectious Diseases. 2023 Apr 1;23(4):393-5.
5. Klein J, Wood J, Jaycox JR, Dhodapkar RM, Lu P, Gehlhausen JR, Tabachnikova A, Greene K, Tabacof L, Malik AA, Silva Monteiro V. Distinguishing features of long COVID identified through immune profiling. Nature. 2023 Nov 2;623(7985):139-48.
6. Proal, A. et al.Targeting the SARS-CoV-2 reservoir in long COVID; Lancet Infect Dis.2025 May;25(5);e294-e306.
7. Geng LN, Bonilla H, Hedlin H, Jacobson KB, Tian L, Jagannathan P, Yang PC, Subramanian AK, Liang JW, Shen S, Deng Y. Nirmatrelvir-ritonavir and symptoms in adults with postacute sequelae of SARS-CoV-2 infection: the STOP-PASC randomized clinical trial. JAMA Internal Medicine. 2024 Sep 1;184(9):1024-34.
8. Sawano M, Bhattacharjee B, Caraballo C, Khera R, Li SX, Herrin J, Christian D, Coppi A, Warner F, Holub J, Henriquez Y. Nirmatrelvir–ritonavir versus placebo–ritonavir in individuals with long COVID

in the USA (PAX LC): a double-blind, randomised, placebo-controlled, phase 2, decentralised trial. The Lancet Infectious Diseases. 2025 Apr 3.

9. Pan H, Peto R, Restrepo AM, Preziosi MP, Sathiyamoorthy V, Karim QA, Alejandria M, García CH, Kieny MP, Malekzadeh R, Murthy S. Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses. The Lancet. 2022 May 21;399(10339):1941-53.
10. Pridgen WL, Duffy C, Gendreau JF, Gendreau RM. A famciclovir + celecoxib combination treatment is safe and efficacious in the treatment of fibromyalgia. Journal of Pain, 2017:10 451–460.
11. Duffy C, Pridgen WL Whitley RJ. Gastric herpes simplex virus type 1 infection is associated with functional gastrointestinal disorders in the presence and absence of comorbid fibromyalgia: a pilot case–control study. Infection. April 21, 2022 online.
12. Ghandi J, Gaur N, Khera L, Kaul R, Robertson ES. COX-2 induces lytic reactivation of EBV through PGE2 by modulating the EP receptor signaling pathway. Virology. 2015.05.006.
13. Yehong L, Li S, Wang Z. The Role of Cyclooxygenase in Multiplication and Reactivation of HSV-1 in Vestibular Ganglion Cells. ScientificWorldJournal. 2014:2014:912640.
14. Alfajaro MM, Choi JS, Kim DS, Seo JY, Kim JY, Park JG. Activation of COX-2/PGE2 Promotes Sapovirus Replication via the Inhibition of Nitric Oxide Production. Journal of Virology. February 2017 Volume 91 Issue 3 e01656-16.
15. Inglot AD. Comparison of the antiviral activity in vitro of some non-steroidal anti-inflammatory drugs. J Gen Virol. 1969;4(2):203–214.
16. Higaki S, Watanabe K, Itahashi M, Shimomura Y. Cyclooxygenase (COX)-inhibiting drug reduces HSV-1 reactivation in the mouse eye model. Curr Eye Res. 2009;34(3):171–176.
17. Gebhardt BM, Varnell ED, Kaufman HE. Inhibition of cyclooxygenase 2 synthesis suppresses Herpes simplex virus type 1 reactivation. J Ocul Pharmacol Ther. 2005;21(2):114–120.
18. Ghaznavi H, Mohammadghasemipour Z, Shirvaliloo M, Momeni MK, Metanat M, Gorgani F, et al. Short-term celecoxib (celebrex) adjuvant therapy: a clinical trial study on COVID-19 patients. Inflammopharmacology. 2022; 30(5): 1645–1657.
19. Peluso MJ, Ryder D, Flavell R, Wang Y, Levi J, LaFranchi BH, Deveau TM, Buck AM, Munter SE, Asare KA, Aslam M. Multimodal molecular imaging reveals tissue-based T cell activation and viral RNA persistence for up to 2 years following COVID-19. Medrxiv. 2023 Jul 31.
20. Deng X, StJohn SE, Osswald HL, O'Brien AO, Banach BS, Sleeman K. Coronaviruses Resistant to a 3C-Like Protease Inhibitor Are Attenuated for Replication and Pathogenesis, Revealing a Low Genetic Barrier but High Fitness Cost of Resistance. Virol. 2014 Oct; 88(20): 11886–11898.
21. Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. Journal of manipulative and physiological therapeutics. 2004 Jan 1;27(1):26-35.
22. Geisser ME, Clauw DJ, Strand V, Gendreau RM, Palmer R, Williams DA. Contributions of change in clinical status parameters to Patient Global Impression of Change (PGIC) scores among persons

with fibromyalgia treated with milnacipran. PAIN®. 2010 May 1;149(2):373-8.
23. Davis HE, McCorkell L Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. Nature Reviews Microbiology. 2023 volume 21, pages133–146.

Figures

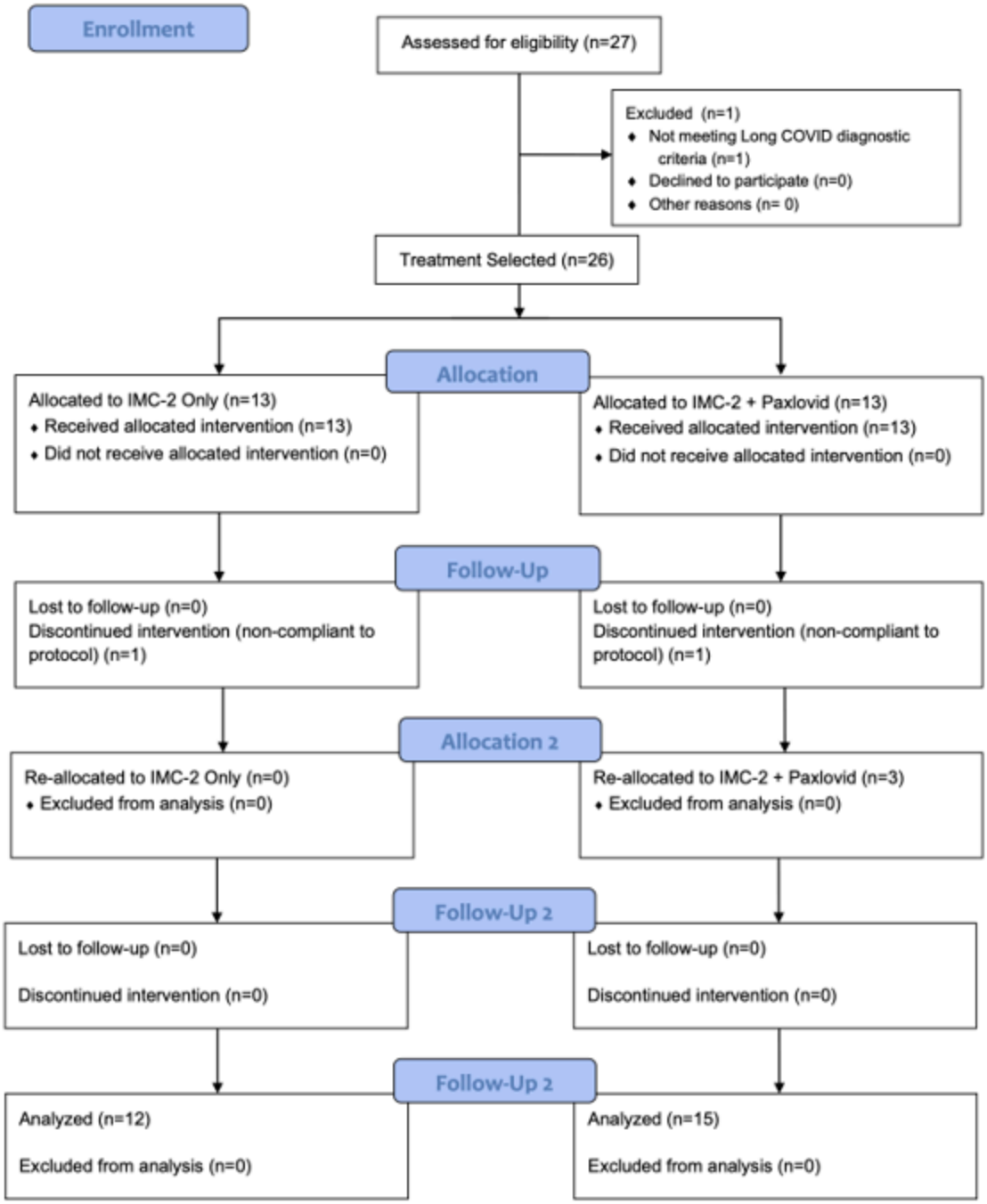

Figure 1

CONSORT Diagram of case series patients

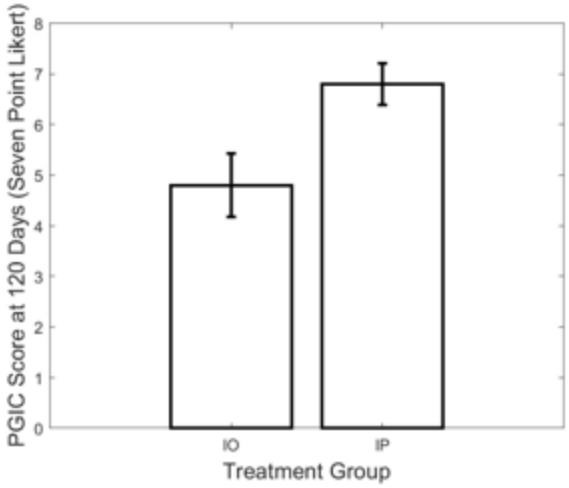

Figure 2

PGIC for fatigue improvement at Day 120 for IO compared with IP

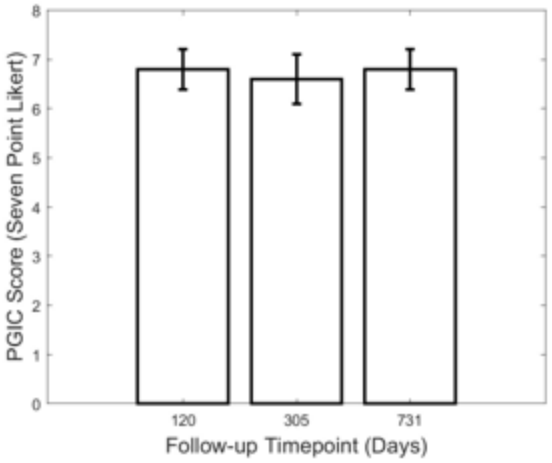

Figure 3

PGIC for fatigue improvement for patients on the IP protocol at 120-, 305- and 720-day follow-up timepoints