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Improvement in Long COVID Symptoms in Two Individuals Treated with Baricitinib

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Abstract

Long COVID is a potentially disabling syndrome that currently lacks effective treatments. We describe two individuals with Long COVID-associated arthralgias, anginal chest pain and evidence of sub-endocardial ischemia by adenosine-stress cardiac magnetic resonance, whose symptoms improved with the Janus-Kinase 1/2 inhibitor baricitinib.

Keywords: Baricitinib; Long Covid; Post Covid-19 Condition; Post-Acute Sequelae of SARS-Cov-2 (PASC); Angina; Arthralgia.

Introduction

Long COVID is a persistent, severely debilitating systemic disease affecting 5-10% of individuals in the post-acute phase of SARS-CoV-2 infection [1,2]. The biology is incompletely understood, the diagnosis is challenging, and there are currently no agreed upon treatments. The proposed pathophysiology includes systemic immune dysregulation, autoimmunity, microvascular dysfunction, gut dysbiosis, viral antigen persistence, herpesvirus reactivation and alterations in levels of regulatory hormones [3,4]. Baricitinib (Olumiant; Lilly), a Janus Kinase-1/2 (JAK1/2) inhibitor approved for rheumatoid arthritis and alopecia areata [5], improves clinical recovery and survival in severe acute COVID-19 [6-8], and is being evaluated for Long COVID in a randomized, double-blinded, placebo-controlled trial (NCT05858515). We describe two individuals with Long COVID with persistent, highly debilitating angina and inflammatory arthralgias whose symptoms improved after receiving baricitinib (Figure 1).

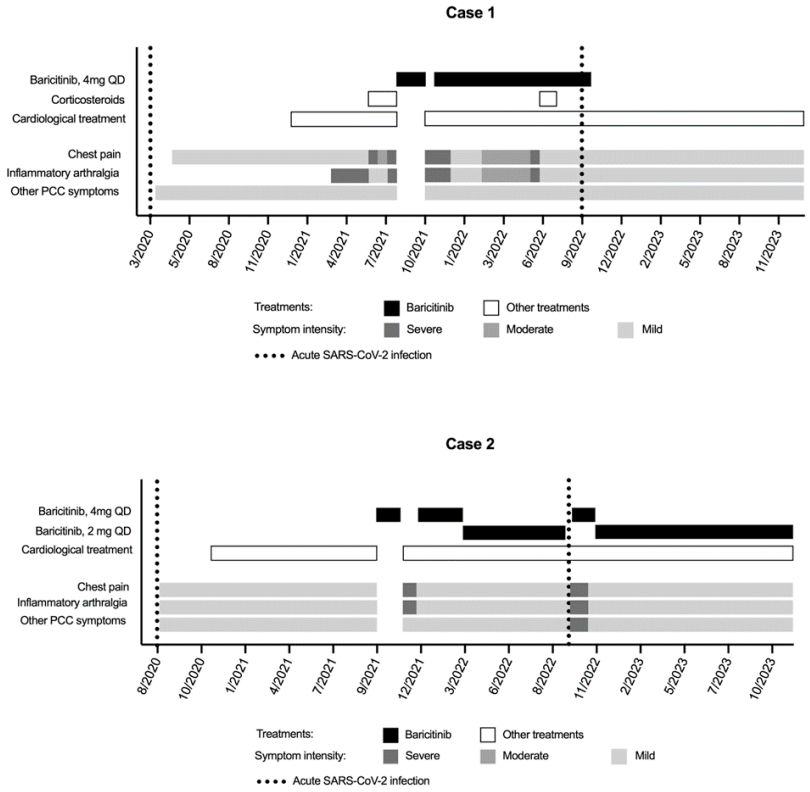

Figure 1: Longitudinal evolution of the two cases. Grey horizontal bars represent presence of symptoms. The intensity of grey is proportional to the intensity of each symptom or group of symptoms, categorized as mild (does not affect daily activities), moderate (daily activities partly affected) or severe (daily activities severely affected). Black horizontal bars represent exposure to baricitinib, either at 4 or 2 mg QD dose. White horizontal bars represent exposure to other treatments to control Long COVID symptoms. Vertical dashed lines indicate acute SARS-CoV-2 infection.

Case 1

A 41-year-old woman tested positive for SARS-CoV-2 (RT-PCR; 3/2020). Medical history was notable for a first-trimester spontaneous abortion (2014), pelvic inflammatory disease following hysterectomy (2015), and seronegative metacarpophalangeal arthritis with an autoimmune evaluation not suggestive of an autoimmune disorder as the cause of her arthritis. She had no cardiovascular risk factors. Family history was notable for rheumatoid arthritis.

Acute COVID-19 symptoms included anosmia, fever, arthralgia, myalgia, and shortness of breath. She was hospitalized for 7 days and treated with hydroxychloroquine/azithromycin (5 days). Acute phase reactants, including C-reactive protein (CRP), interleukin-6, fibrinogen, and erythrocyte sedimentation rate (ESR) remained within normal ranges.

During the post-acute phase, she continued experiencing low-grade fever, dyspnea, hypotension, bradycardia, and chest pain (Table 1). Initially, chest pain exhibited features suggestive of pericarditis, which improved with NSAIDS and colchicine, and later evolved into angina pectoris. Laboratory results showed lymphopenia (500 cells/μL), gradually improving to 900 cells/μL. D-Dimer, ferritin, troponin, liver/kidney functions, rheumatoid factor, and antinuclear antibodies remained within normal range.

In 12/2020, anti-anginal treatment was started (ranolazine 375mg BID and nitroglycerin). Transthoracic echocardiography showed normal left ventricular function and coronary angiography by computed tomography (CT) showed no evidence of coronary artery disease. An adenosine stress cardiac magnetic resonance imaging (MRI) (12/2021) revealed an inducible defect in circumferential sub endocardial perfusion and no signs of myocarditis were found. Given the normal coronary arteries, this finding could be consistent with underlying microvascular disease. Due to headaches, she was switched from nitrates to diltiazem, which was gradually increased to 90mg TID. Subsequently, the following medications were titrated to maximum levels: ranolazine: 750 mg BID; diltiazem: 120 mg BID; nitroglycerine: 100 mg (40-40-20mg) TID.

In 3/2021, she developed inflammatory arthralgias (predominantly at night, at rest) affecting bilateral wrists, shoulders, hips, and ankles, without signs of arthritis. By 6/2021, her arthralgias and chest pain worsened, with symptoms at rest. Oral prednisone 1 mg/kg (50mg) daily was initiated. This significantly reduced arthralgias but only partially alleviated chest pain. In 7/2021, prednisone was reduced to 40 mg daily, resulting in recurrence of both joint and chest pain. Consequently, the dose was increased to 60 mg daily. To minimize chronic corticosteroid exposure, baricitinib (4 mg QD) was introduced on 7/2021.

One week after initiating baricitinib, there was a marked improvement in functional status and all clinical symptoms, including marked reductions in joint and chest pain. As a result, the patient was able to reduce and eventually stop corticosteroids (8/2021), and reduce and discontinue antianginal medications. She successfully returned to work and engaged in low-intensity sports.

In 10/2021, after three months of treatment, baricitinib was discontinued. Within 48 hours, there was a dramatic clinical deterioration, characterized by a recurrence of anginal chest pain and symmetric, diffuse arthralgia, similar to previous symptoms. Consequently, baricitinib (4 mg QD) was resumed (11/2021). Clinical improvement was observed after approximately 30 days. This allowed for a reduction in anti-anginal medication.

In 2/2022, while still on baricitinib 4 mg, the patient experienced worsening of angina and arthralgia (without a clear trigger), which intensified in 5/2022. A short course of prednisone was prescribed until 7/2022, resulting in an upper respiratory tract infection and labial herpes simplex. In 9/2022, the patient had a SARS-CoV-2 reinfection and received treatment (nirmatrelvir-ritonavir; 300/100 mg BID, 5 days). Despite continued treatment with baricitinib, she continued experiencing angina with minor exertion, arthralgia, and diarrhea. The role of ongoing baricitinib treatment was unclear, and her doctors advised its discontinuation.

In 1/2023, the patient underwent cardiology follow-up, which showed progressive improvement of symptoms even without baricitinib. However, she continued to require treatment for angina. In 3/2024 she was receiving bisoprolol: 2.5 mg QD; trimetazidine 20 mg TID; nitroglycerine: 20 mg BID; ranolazine: 750 mg QD; colchicine: 0.5 mg BID.

Interestingly, there were no changes in persistent symptoms following any of her three SARS-CoV-2 vaccinations (Cominarty®;3/2021 and Moderna®;12/2021).

	CASE 1	CASE 2
Sex	Female	Female
Age	41	44
Occupation	Physician	Physician
Allergies	No	Yes (anaphylaxis grade III)
Family history of heart disease	No	No
Comorbidity	Abortion, pelvic inflammatory disease, metacarpophalangeal arthritis	Abortion and thrombophilia associated with pregnancy, bronchial hyperreactivity, laparoscopic cholecystectomy and abdominal eventration
Date of SARS-CoV-2 infection	March 2020 September 2022	August 2020 September 2022
Treatment of acute SARS-CoV-2 infection	1st infection: hydroxychloroquine and azithromycin 2nd infection: nirmatrelvir/ritonavir	1st infection: none 2nd infection: nirmatrelvir/ritonavir
Acute COVID-19 symptoms	Anosmia, fever and arthralgia, myalgia, and shortness of breath	Anosmia, ageusia, headache, fever, arthralgia, myalgia, dry cough, fatigue,
Persistent Long COVID symptoms	Myalgia, fatigue, low-grade fever, aphonia, dyspnea, bradycardia, hypotension, syncope, chest pain, inflammatory arthralgia, skin alterations and hair loss.	Right hypochondria pain, chest pain, inflammatory arthralgia, myalgia, mild neurocognitive complaints, hands paresthesia, fatigue, headache, and shortness of breath
Acute phase reactant parameters (CRP, IL-6, fibrinogen, ESR)	Normal	Normal
Other biomarkers (ANA, RF, HLA-B27)	Negative	Negative
Transthoracic echocardiography	Normal	Normal
Computerized tomography coronary angiogram	No coronary lesions	No coronary lesions
Computerized tomography angiography	No pulmonary thromboembolism	No pulmonary thromboembolism
Cardiac MRI with adenosine (140 ug/kg/min)	Inducible defect of circumferential subendocardial perfusion	Inducible defect of circumferential subendocardial perfusion
Corticosteroid treatment	Prednisone 1mg/kg: 50mg	No
Cardiac treatment	Diltiazem 120 mg BID, nitroglycerin 100 mg QD, ranolazine 750 mg BID	Aspirin 100 mg QD, nitroglycerin 20 mg TID ranolazine 750 mg BID, bisoprolol 2.5 mg QD, amlodipine 5 mg BID, trimetazidine 20 mg TID
Immunomodulatory treatment	Baricitinib 4mg QD	Baricitinib 4mg QD
PCFS scale after 1st SARS-CoV-2 infection	3	3

PCFS after first baricitinib exposure	0	0
PCFS after second baricitinib exposure	2	2

Table 1: Characteristics of the two cases.

Case 2

A 44-year-old woman contracted SARS-CoV-2 in 8/2020, confirmed by RT-PCR. During the acute phase, she experienced anosmia, ageusia, fever, arthralgia, myalgia, fatigue, and anginal chest pain. Acute phase reactants were within normal ranges. She did not receive specific antiviral treatment. Medical history included anaphylaxis (2014), bronchial hyper reactivity, thrombophilia following fetal demise at 27 weeks of gestation (2010), laparoscopic cholecystectomy (2017), and intervention for abdominal event ration (2018). She had no family history of heart disease.

In the post-acute phase, she continued to experience persistent symptoms (Table 1), including right hypochondrium pain, chest pain, inflammatory arthralgia, myalgia's, memory loss, hand paraesthesia's, fatigue, headache, and shortness of breath. Laboratory tests remained within normal ranges (blood count, ferritin, troponin, liver and kidney function, autoimmunity screening, and an immunodeficiency study).

In evaluation of persistent anginal chest pain, a transthoracic echocardiography and CT coronary angiography did not reveal any abnormalities and ruled out pulmonary thromboembolism. An adenosine stress cardiac MRI (140 ug/kg/min) revealed an inducible sub endocardial perfusion defect, almost circumferential, which strongly suggested microvascular dysfunction. Treatment for microvascular angina included aspirin 100mg QD; nitroglycerin 20 mg TID; ranolazine 750 mg BID; bisoprolol 2.5 mg QD; amlodipine 5 mg BID; trimetazine 20 mg TID.

Initially, the patient experienced mild improvement in symptoms. In 9/2021, baricitinib (4 mg QD) was introduced, leading to significant improvement in anginal symptoms within 48 hours, allowing gradual reduction and eventual withdrawal of all antianginal medications. Although arthralgias also improved, they persisted. The patient's clinical progress enabled her to engage in activities including climbing stairs (five floors consecutively) and 20 minutes of aerobic exercise without angina.

In 11/2021, baricitinib was discontinued, resulting in abrupt recurrence of fatigue, dyspnea, arthralgia, and angina. Upon resuming baricitinib (4 mg QD; 12/2021), the patient's symptomatology improved again over the following month. Although antianginal treatment was reduced, it could not be completely stopped. In 3/2022, baricitinib was further reduced to 2mg. The patient's condition remained unchanged compared to treatment with baricitinib 4mg.

In 9/2022, a SARS-CoV-2 reinfection was treated with nirmatrelvir/ritonavir. This coincided with a worsening of persistent Long COVID symptoms, necessitating an increase in the baricitinib dose to 4 mg daily. Subsequently (11/2022), baricitinib was reduced back to 2mg, and has been maintained at this dose. In 12/2023, due to another acute infection, nirmatrelvir-ritonavir was initiated. As of 3/2024 the patient's clinical situation is stable, with microvascular angina classified as functional class II (NYHA), and fatigue occurring with light exertion, limiting basic daily activities.

The SARS-CoV-2 vaccinations received by the patient were: First dose (Cominarty®;1/8/2021, second dose (Cominarty®;1/29/2021, resulting in significant worsening of symptoms, particularly in angina pectoris), third dose (Moderna®; 1/1/2022, leading to slight worsening of symptoms for approximately two weeks, followed by stabilization to the previous state).

Discussion

We present two cases of Long COVID in patients exhibiting microvascular angina, inflammatory arthralgia, and other persistent symptoms. Upon initiating baricitinib, both experienced improvement in overall disease severity. Upon discontinuation, symptoms worsened. A second exposure to baricitinib improved, but did not eliminate symptoms completely.

Baricitinib reduces phosphorylation and activation of STATs. In vitro studies demonstrate that baricitinib decreases spike-specific responses by reducing expression of cytokines including IL-17, IL-1β, IL-6, IFN-γ, TNF-α [9]. These findings have also been observed in patients with acute COVID-19, and baricitinib has been shown to be of benefit in dampening the acute inflammatory response during the acute phase of infection [6,7,10].

Immune dysregulation is a key mechanism proposed in the pathophysiology of Long COVID [11], involving cytokine alterations [12,13], and increase in CD4+ and CD8+ T-cell exhaustion [14,15]. Recent findings in patients suffering from Long COVID highlight activation of the complement cascade and the endothelium as part of the pathobiology leading to

microangiopathic complications and organ dysfunction [16]. Despite the complexities and heterogeneity of Long COVID, immune dysregulation remains a significant driver of the disease process in most models [17-19]. Therefore it is hypothesized that baricitinib may be of benefit in directly targeting immune dysregulation during the post-acute phase of COVID-19.

The clinical outcomes in these two cases provide anecdotes of patients experiencing improvement in functional status with immunomodulator therapy. In both cases, clear symptom improvement appeared to coincide with initial administration of baricitinib, but was transient and concurrent with other treatments. Withdrawal of baricitinib led to recrudescence of symptoms, and re-exposure to the drug improved but did not eliminate them completely. In both cases, myocardial ischemia was evident in stress magnetic resonance, but follow-up imaging was declined by both patients because of concerns about recurrence of anginal pain.

There remain no agreed upon treatments for Long COVID. These anecdotes suggest that further investigation of immunomodulator therapy for this condition is warranted. Randomized trials will be needed to address confounding and establish the efficacy and safety of baricitinib. The National Institute on Aging (NIA) has funded a phase III investigation (baricitinib versus placebo; REVERSE-LC (NCT05858515)). Such efforts will be critical in elucidating the role of immune dysfunction in Long COVID and determining whether intervention on these pathways confers benefits for people experiencing this disabling condition.

Author contributions: GL and LM were the physicians taking care of the patients and collected clinical, radiological and laboratory data. GL, VC, EWE, RP, LM drafted the manuscript. All authors provided significant edits and scientific input and approved the manuscript.

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