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Letter to the Editor

Understanding immune dysregulation in post-acute sequelae of COVID-19 (PASC)—The hunt for effective treatments

Dear Editor,

Fernandez-de-las-Peñas and colleagues reported the alarmingly high persistence of post-COVID symptoms 2 years after acute infection with SARS-CoV-2.[1] The SARS-CoV-2 pandemic triggered an unprecedented mobilization of the global scientific community leading to the rapid availability of direct acting antivirals and vaccines. The introduction of these antivirals and vaccines successfully limited the spread of new cases of SARS-CoV-2 and provided options for treating the infection. However, despite these advances there is still a worryingly high number of individuals with post-acute sequelae of COVID-19 (PASC), also commonly known as long COVID. This chronic condition is characterized by heterogenous, multi-systemic, signs and symptoms that continue after the initial acute phase of the SARS-CoV-2 infection has resolved. PASC may worsen over time, fluctuate in severity, and in some individuals can be highly debilitating and even life-threatening. It is estimated that in 2022, 6.9% of adults living in the USA had ever suffered PASC and 3.4% were experiencing PASC at the time of the interview with more women (8.5%) than men (5.2%) reported ever suffering PASC.[2]

Compared to a control group receiving supportive treatment alone, the occurrence of PASC is reduced by 27.5% among individuals receiving antiviral treatments during the early stages of SARS-CoV-2 infection (OR = 0.725; 95% CI = 0.409–0.747) with a 29.7% reduction in the risk of PASC-associated hospitalization and mortality (OR = 0.721; 95% CI = 0.697–0.794).[3] In a different study among double-vaccinated versus unvaccinated participants PASC was reported by 9.5% of vaccinated individuals and 14.6% unvaccinated individuals (aOR = 0.59; 95% CI = 0.50–0.69).[4]

Despite the positive impact of antiviral treatments and vaccinations on the occurrence of PASC it remains a significant burden for many people. In the study reported by Fernandez-de-las-Peñas and colleagues they describe the results from a meta-analysis across 12 studies including 7912 COVID-19 survivors.[1] They summarized post-COVID symptoms approximately 2 years after infection and reported that the most prevalent post-COVID symptoms were fatigue (28.0%; 95% CI = 12.0–47.0), cognitive impairment (27.6%; 95% CI = 12.6–45.8), and pain (8.4%; 95% CI = 4.9–12.8). Thus not only is PASC a debilitating and potentially life-threatening condition it can persist for at least two years in some individuals. Considering the huge numbers of people suffering PASC globally, and its persistence over time, there is a considerable burden of disease associated with PASC, and an urgent need to better understand and ultimately treat PASC.

A significant barrier to developing effective treatments for PASC is that currently the exact pathophysiology of PASC is poorly understood. However, most theories suggest that PASC is driven, at least in part, by immune dysregulation. We performed an exploratory study in 55 individuals with PASC who were randomly assigned to receive either leronlimab or placebo.[5] Leronlimab is an investigational CCR5-specific humanized IgG4 monoclonal antibody. CCR5 plays a role in a number of diseases including acute severe COVID-19 where leronlimab is believed to resolve inappropriate inflammation through its interaction with CCR5.[6] We postulated a priori that PASC is mediated by persisting inflammation after acute COVID-19. We explored changes in symptom severity scores through day 56 for 24 common symptoms reported in individuals with PASC. Overall the mean symptom score changes from baseline to the latest available time point from day 30–56 was −16.0 and −12.0 for leronlimab and placebo, respectively. Of importance a greater numerical decrease in symptom severity score was seen for 19 of the 24 symptoms for leronlimab treated individuals compared to placebo treated individuals (Fig. 1). However, it is important to note that the trial was not powered for statistical comparisons between treatments. The trial also observed significantly increased blood cell surface CCR5 from baseline to day 56 in leronlimab treated symptomatic responders but not in leronlimab treated non-responders or those participants who received placebo. To our surprise, rather that showing that PASC is mediated by persisting inflammation after acute COVID-19 we had to conclude that at least in some individuals with PASC there is an unexpected immune downmodulation prior to leronlimab treatment which was normalized after leronlimab treatment.[5] Interestingly, this could be an explanation for the widely reported proposed link between Epstein-Barr Virus (EBV) reactivation among individuals with PASC. A further signal that immune dysregulation is a central feature of PASC is that emerging data suggests that autonomic dysfunction, which is commonly associated with other autoimmune and chronic inflammatory diseases, is commonly seen in individuals with PASC. Clearly the results of our trial are intriguing and suggest that immune dysregulation is a consistent factor in PASC. Our results, and those of others, strongly suggest that more efforts are needed to understand the role of the immune system in PASC and to explore the potential role of immunomodulators in the treatment of PASC.

While the results of our trial are certainly encouraging what is less encouraging is the apparent lack of mobilization of the wider scientific community to find an effective treatment for PASC. Although we must acknowledge that some studies have proposed potentially effective treatments including, but not limited to, nutraceuticals,[7] hyperbaric oxygen,[8] and home-based, supervised, group physical and mental health rehabilitation.[9]

Worryingly a recent study by Bonuck and colleagues explored burden-commensurate funding for the top YLD (years of health life lost due to disability) conditions and for female versus male dominant conditions and found that PASC research funding is lagging behind its disability burden.[10] The authors also pointed out that females are disproportionately affected by PASC and that there is

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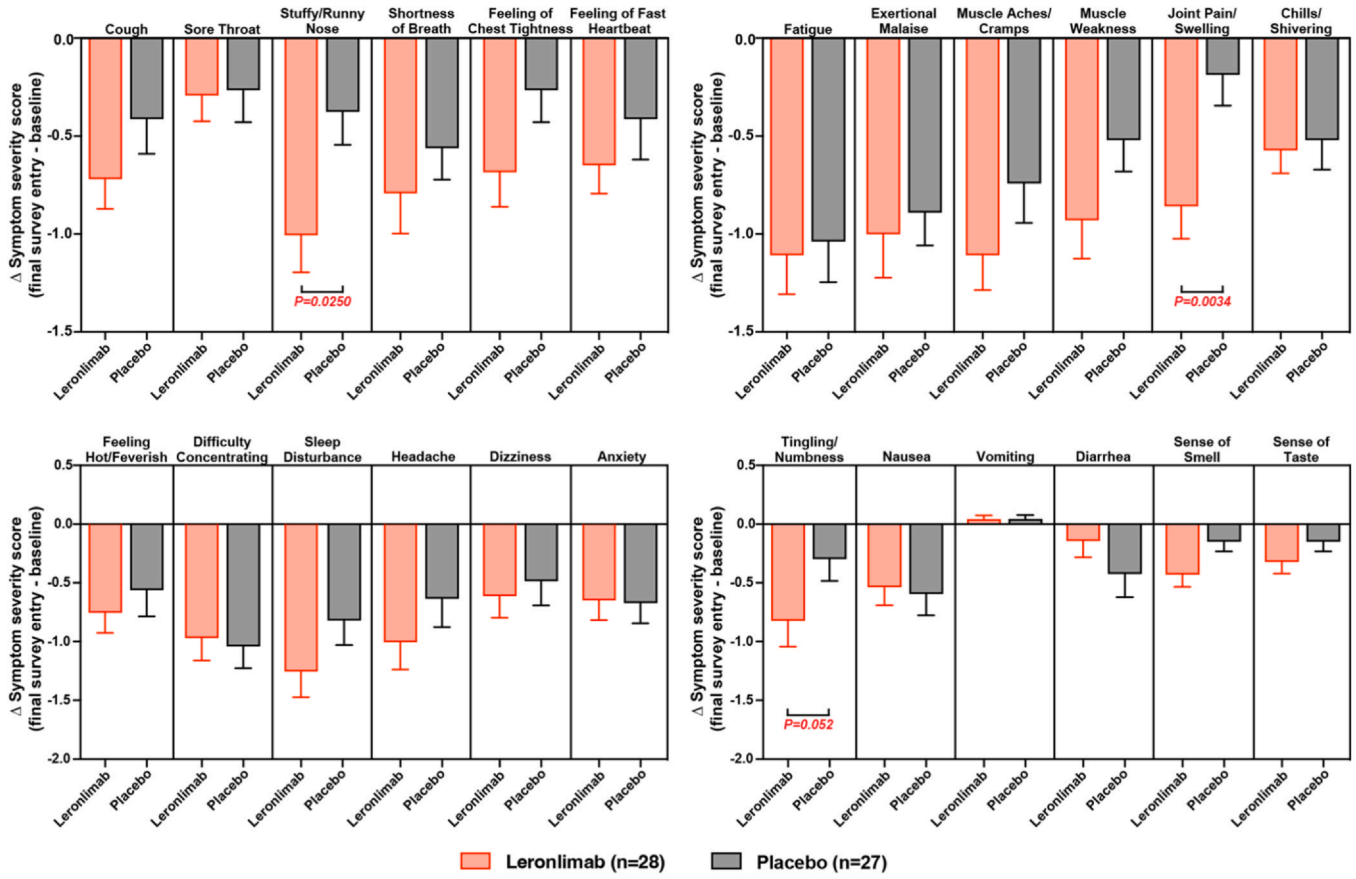

Fig. 1. Change in symptom severity from baseline up to day 56 for subjects receiving leronlimab or placebo. From an article in the journal Clinical Infectious Diseases, published by Oxford University Press.[5]

evidence to suggest that other female dominated conditions also suffer from less research funding.[10]

Taken together we can be encouraged by the tremendous advances made in the last 3–4 years which has led to the availability of antiviral treatments and vaccines for SARS-CoV-2 but research into PASC needs to be dramatically increased and prioritized in line with the significant burden of disease. Immunomodulators remain potentially effective treatments for PASC but without a concerted effort from funding agencies and researchers alike progress will lag behind and PASC will remain a huge burden for millions of people around the world.

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Declaration of Competing Interest

OOY serves on the CytoDyn Scientific Advisory Board and is a scientific consultant (compensated in stock options and cash) for CytoDyn. OOY is co-founder and board member for CDR3 Therapeutics Corp (stock). OOY is on the Board of Directors for Applied Medical Inc (stock and cash). NBG serves on the CytoDyn Scientific Advisory Board with stock option.

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