Pharmacological trials for long COVID: first light at the end of the tunnel

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There is growing and overwhelming evidence that a group of patients do not fully recover from SARS-CoV-2 infection, but develop a set of long lasting and debilitating multi systemic signs and symptoms.[1] This condition is known as post-COVID condition (PCC) or long COVID, as initially named by patients themselves, and has been officially recognized by the World Health Organization in October 2021. The overall impact of long COVID has not yet been clearly established, but estimates suggest a massive direct and indirect negative impact on the society and their economy, as patients require complex and expensive support from national health systems, and their ability to return to work (including for healthcare professionals) is usually impaired.[2–4]

So far, research efforts have focused initially on understanding the epidemiological burden of long COVID and then on understanding its causes and discovering possible biomarkers. While such efforts have been welcomed by the scientific and patients' communities, patients have also complained about the lack of therapies and pharmacological trials. Fortunately, the road is now turning around and the results of a methodologically rigorous pharmacological trial have been just published in this issue of *The Lancet Regional Health-Europe*, raising hopes for a new era in long COVID research.[5]

Hansen at al performed a placebo-controlled, double-blind, 2×2 crossover interventional trial in Denmark, randomly assigning patients with long COVID to receive oral coenzyme Q10 (CoQ10) capsules at a dose of 500 mg/day or placebo for six weeks, with crossover treatment after a four-week washout period.[5] The primary endpoint was the change in the number and/or severity of long COVID related symptoms after the six-week intervention compared with placebo. The crossover design was performed to eliminate between-subject variability. The rationale for using CoQ10 was based on a solid organic hypothesis raised by previous studies that long COVID, or at least some of its symptoms, may be due to a mitochondrial dysfunction and could therefore be treated with high doses of CoQ10.[5] Unfortunately, there was no difference between the treatment and placebo groups, suggesting that CoQ10 may not be the best treatment for patients with long COVID and should not be prescribed outside of clinical trials. However, despite the negative findings, this study carries several positive lessons for future studies that should allow clinicians and patients, to be optimistic about the future treatments for Long COVID.

The first positive takeaway is that for patients, who have been struggling for at least two years to have their disease recognized as a real illness, participating in clinical trials, whatever is their final result, is an important first step towards accessing appropriate, comprehensive and multidisciplinary care.

Secondly, patients' symptoms often lead them to try to self-medicate or to seek unproven treatments.,[6] and since nutraceutical companies are producing new products or promoting old ones, claiming to improve long COVID symptoms, even though positive in vitro and in vivo effects have not yet been demonstrated,[7] having negative results from clinical trials is useful to inform patients and companies.

Third, there are some aspects of this clinical trial that could be improved before ruling out CoQ10 as a treatment for long COVID. Patients have been enrolled at different time points after the initial infection, some of them several months later. As such, given the plausible hypothesis of a mitochondrial dysfunction in COVID-19,[5] it cannot be excluded that earlier treatment with CoQ10 may be more effective, as a chronic malfunction in a biological system may be more difficult to be treated.

Fourth, it is unlikely that a single intervention can be effective in treating such a complex systemic condition. Recent research considers long COVID to be a complex disease in which multiple different mechanisms triggered by the initial infection in a susceptible host, may play significant roles.[8] Indeed, immunological imbalances, chronic endothelitis with circulating micro-clots, and intestinal dysbiosis have been documented in patients with long COVID.[8] Therefore, it is crucial that trials involving a multipharmacological approach are implemented.

Finally, with the increasing number of cases different phenotypes of long COVID have been

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identified,[7] as has also been described in Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS),[9] a similar post-viral condition. It is possible that patients with specific phenotypes of long COVID (e.g. those with prevalent cardio-respiratory, gastrointestinal, musculoskeletal or neurocognitive impairments) may benefit from different interventions, and therefore trials should focus on defining better inclusion criteria to select patients according to their predominant symptomatology.

Hopefully, this trial will open a new era in long COVID care, which will probably also indirectly benefit the millions of neglected patients with ME/CFS. Importantly, there is clear evidence that long COVID can also affect children, although it is less frequent and usually less severe compared to adult long COVID, and efforts should be made to develop similar trials in children.[7,10]

The huge positive medical and psychological impact that trials can have on the long COVID community, will hopefully lead governments, public and private funders, and policy makers, to follow the path opened by Hansen and colleagues to conduct pharmacological trials for patients with Long Covid.

Declaration of interests

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