COVID-19: Social distancing, ACE 2 receptors, protease inhibitors and beyond?

Sir

I am most grateful to Dr Stein for his thoughtful and considered response to my recent letter.1 However, completely as he predicted, his answers only raised more questions.

I was struck by the analysis of the known mortality data from COVID-19. It is interesting that for a respiratory pathogen, risk of mortality seems to be lower for those with underlying respiratory disease than with pre-existing cardiac pathology. Moreover, the data cited by Dr Stein suggest that pre-existing diabetes is a higher risk for mortality than lung disease, and that pre-existing hypertension confers almost the same risk of death from COVID-19 as underlying lung disease. These findings are unexpected, and surely worthy of further exploration.

In his original editorial,2 Dr Stein pointed to the fact that modern science has the ability to evaluate new pathogens more rapidly than was ever the case previously. Consequently, much is now already established about the molecular biology surrounding SARS-Cov-2, the viral pathogen associated with COVID-19.

SARS-Cov-2 appears to need to bind to the ACE 2 receptor to enable it to infect host cells, coupled with a reliance on the cellular serine protease TMPRSS2 which also seems to be a determinant of the viruses ability to infect cells.3 These authors seem to point to the possibility that the clinically proven serine protease inhibitor camostat mesylate, which is active against TMPRSS2 partially blocked SARS-Cov-2 entry into cells and is thus a potential target as an agent to mitigate the impact of SARS-Cov-2 in individuals affected by COVID-19. They note that at present this agent is licenced for human use in Japan to treat an unrelated condition.

I would be most interested in Dr Stein’s observation on whether urgent trials of this agent in an attempt to combat the rapid advance on COVID-19 are merited?

Returning to the mortality data cited by Dr Stein, the potential link between ACE 2 receptors, cardiac disease, diabetes and hypertension perhaps also merits more thought. In each of these groups of patients, treatment with agents which have an impact on the Renin-Angiotensin System (RAS): ACE inhibitors (ACEI) or angiotensin receptor blockers (ARB) is very common. It has been shown that these treatments can up-regulate ACE 2 receptor expression in humans,4,5 and it is thus theoretically possible that pre-existing use of these drugs might predispose a person to infection with a greater viral load of SARS-Cov-2 as a result of greater ACE 2 receptor expression. Equally, it is possible that intervening with an agent which inhibits the ACE receptors may confer therapeutic benefit in those suffering from COVID-19.5 However, one cannot help but speculate that the increased and somewhat unexpected mortality risk from COVID-19 in those groups where a high prevalence of ACEI and ARB treatment might be expected is somewhat troubling.

In this context, current data appear to conflict. There is some small-scale evidence that prior use of ACEI/ARB drugs in those with cardiovascular disease did not affect outcomes.6 However, this was a very small study and it would be helpful if the data in respect of any risk imposed by pre-existing ACEI/ARB therapy could now be verified given the much larger databases that must now be available to the global scientific community since this publication early in the evolution of the COVID-19 pandemic. Other authors have speculated that use of ACEI/ARB might actually be a potentially beneficial intervention in those, presumably ACEI/ARB-naïve patients, who develop COVID-19.7,8

What seems clear, given the conflicting data, is that the scientific world has not yet fully evaluated this important question and yielded a definitive answer.

Whether prior use of ACEI/ARB increases risk from COVID-19, or indeed use of these drugs in treating those with severe infection might in fact improve mortality rates, are surely questions that should be urgently addressed as the pandemic of COVID-19 progresses rapidly?

Returning to the known molecular biology relating to SARS-Cov-2, there is speculation that the use of other agents: cepharanthine (CEP), selamectin and mefloquine hydrochloride are potential drugs for treating 2019-nCoV infection.9 The authors strongly suggest that CEP is a wide-spectrum inhibitor of pan-betacoronavirus, and that a clinical trial of CEP for treatment of 2019-nCoV infection is warranted. Might these drugs offer further potential therapeutic targets in supporting clinicians managing the COVID-19 pandemic?

International governmental response to the developing pandemic have been heterogeneous, and I am therefore naturally concerned to see that Dr Stein’s review of the literature suggests that patients infected with SARS-Cov-2 are known to shed the virus in the prodromal stages, which is presumably before the symptoms have developed, and if so how should this affect global isolation strategies?
In addition, Dr Stein suggests that affected patients may continue to shed the virus beyond the 7th day of infection—is it yet known when an infected person is no longer able to transmit the virus to other susceptible people and if so, should this science guide global isolation precautions?

Present, or recent, international governmental advice has varied from self-isolation from the first day of symptoms for 7 days, to imposed quarantine across an entire region or nation. Given Dr Steins insight into the virology of SARS-CoV-2, what would he recommend should be the global advice on isolation in line with the science associated with COVID-19 and the importance of social distancing measures?

The immediate future with COVID-19 gives natural cause for concern, but it does seem that much is already known about this virus. While there is little, if any, time to run large randomised clinical trials into the potential therapies that might be deployed in the present pandemic, it does seem that the already abundant data available should offer some early indicators and clues to where research should be urgently focused. Given the scale of the pandemic, and given the correct pointers, surely the world’s scientific community is in a unique place to start to guide national and international efforts to combat this disease?

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