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Commentary

Renin Angiotensin System Inhibition as treatment for Covid-19?

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Early in the Covid-19 pandemic, concern abounded that treatment with renin-angiotensin-system (RAS) inhibitors, such as angiotensin converting enzyme (ACE) inhibitors, or angiotensin receptors blockers (ARBs), might increase the risk of infection, severe disease, or death from Covid-19 [1]. This was founded on the observation that SARS-Cov-2 binds to ACE2 as the gateway for entry into cells, further fuelled by speculation based on animal studies, that RAS-inhibition might upregulate the expression of ACE2, facilitating infection [1]. Subsequent cohort studies, provided reassurance that treatment with RAS-inhibitors was not associated with increased risk from Covid-19 [2]. Indeed, some observational studies suggested that treatment with RAS-inhibition might even reduce risk of severe Covid-19 or death [2,3]. Two RCTs evaluated continuation versus acute withdrawal of pre-existing RAS-inhibitor treatment, in patients hospitalised with Covid-19. Both RCTs showed no difference in major Covid-19 outcomes [4,5].

Although concern about RAS-inhibition dominated at the onset of the pandemic, there was a less prominent counter view that RAS-inhibition might be considered as a potential treatment for patients with Covid-19 [6]. This dichotomy of opinion might seem surprising but there is a rational basis for both viewpoints. As with many biological systems, the consequence of RAS system activation is context specific. The RAS system is both complex and dynamic, closely regulated by the balance of activity between ACE and ACE2 [7]. The ACE pathway is best known, and ACE (the target for ACE-inhibitors) cleaves angiotensin-I to generate angiotensin-II, which acts via the angiotensin type-1 (AT-1) receptor (the target for angiotensin receptor blockers – ARBs), to promote pressor, pro-inflammatory, pro-fibrotic and pro-thrombotic activity. Simultaneously but in contrast, the ACE2 (the gateway for SARS-Cov-2 entry into cells) pathway of the RAS system, counteracts the ACE pathway by cleaving angiotensin-II to angiotensin 1-7, thereby reducing angiotensin-II availability to the AT-1 receptor. Furthermore, the resulting angiotensin 1-7, acts via the MAS-receptor, to induce vasodepressor, anti-inflammatory, anti-oxidative, and antiproliferative actions. Thus, the net effect of the RAS-system depends on the balance of ACE versus ACE2 activity.

The binding of the SARS-Cov-2 spike protein to ACE-2 has the potential to disturb this balance, by downregulating ACE2, thereby diminishing the potentially protective effects of the ACE2 pathway in the context of acute inflammation, whilst simultaneously releasing the brake on the pro-inflammatory and pro-thrombotic arm of the RAS system, acting through ACE, angiotensin II and its AT-1 receptor. This concept is beyond hypothetical because in animal models, administration of recombinant SARS virus spike protein alone, in the absence of viral replication, is sufficient to downregulate ACE2 on the surface of pulmonary alveolar cells and induce lung injury [8]. The fact that an ARB was shown to protect the lung in these models where ACE2 has been depleted, supports the concept that lung ACE2 is normally protective and that its depletion allows the unopposed actions of the ACE-angiotensin II-AT-1 receptor arm of the RAS system to induce and/or potentiate lung injury [8]. This may explain the observation in humans, that treatment with ACE-inhibitors or ARBs, is associated with reduced frequency or severity of community acquired pneumonia [9].

Such insights provide a clear rationale for considering inhibitors of the RAS system as potential therapeutics to reduce the severity of Covid-19 disease, especially lung injury. A number of studies have been initiated, designed to either block the potentially deleterious effects of angiotensin II by blocking its production via ACE-inhibition, or its action at the AT-1 receptor with an ARB and/or by augmenting the "protective arm" of the RAS system by delivering recombinant ACE2 to the lung [*NCT04287686*], or stimulating the angiotensin AT-2 receptor [*NCT04452435*].

In *EClinicalMedicine*, Duarte and colleagues report the first phase 2 RCT evaluating treatment of hospitalised Covid-19 patients with an ARB, telmisartan, versus usual care, in an open label study in Argentina [10]. The results are very intriguing. C-reactive protein (CRP), the primary outcome, and predictive of outcomes in Covid-19, was significantly reduced by telmisartan versus usual care. There were also strong signals (albeit based on small numbers) of potential benefit on important secondary outcomes, including ICU admission, time to discharge and death. This is despite the fact that randomisation appeared unbalanced in favour of the standard of care arm, as there were more men and higher baseline CRP levels in patients allocated to telmisartan, both of which are predictors of poorer outcome. Of

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course, the findings of this small phase 2 study should not be over-interpreted and nor do they alone, justify a change in treatment strategy for Covid-19. The findings do, however, provide an important basis to consider angiotensin receptor blockade as a potential therapy for some hospitalised patients with Covid-19, in a formal phase III RCT, to get a definitive answer. The study also had some critical design features that might help drive a beneficial outcome and should influence the design of a future study. First, the patients were treated early, within 4 days of symptom onset and timing of intervention, mindful of proposed pathophysiological mechanisms, is likely to be important. Second, the ARB selected, telmisartan, was used twice daily and at twice the usual maximal dose, and such high doses might be needed to suppress a dysregulated RAS system in Covid-19. Alongside, the intervention appeared safe and well tolerated, although this won't be the case for all hospitalised patients with Covid-19. Finally, the study also provides further scientific evidence that earlier concerns about use of RAS-inhibitors in patients with Covid-19 was unwarranted and may even be beneficial.

Contributors

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Declaration of Competing Interest

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