We hope a novel HCC risk prediction model will be developed in the near future to prioritise treatment in CHB patients who are not currently indicated for treatment even with high risk to develop HCC. The model should properly reflect the adequate association between broad range of HBV DNA levels and HCC risk.

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LINKED CONTENT

This article is linked to Kim et al and Kumar and Mishra papers. To view these articles, visit https://doi.org/10.1111/apt.15725 and https://doi.org/10.1111/apt.15829.

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Letter: ACE2, Rho kinase inhibition and the potential role of vitamin D against COVID-19

The known immunomodulatory roles of vitamin D including the down-regulation of pro-inflammatory cytokines, in particular *via* its inhibitory effects on the activation of the renin-angiotensin system (RAS), have recently raised interest for a possible role of vitamin D in the prevention of COVID-19.[1]

RAS plays a role in the COVID-19 infection process *via* angiotensin converting enzyme 2 (ACE2), the entry point of SARS-CoV2. The involvement of ACE2 has given rise to conflicting suggestions on ACE2 contribution in the treatment of COVID-19. The protective role of ACE2 in SARS-CoV2 infection process could, in fact, be better understood by understanding the protective role of the anti-inflammatory and vasodilating ACE2-Angiotensin (Ang) 1-7 axis of RAS vs the classical pro-inflammatory and vasoconstricting ACE-Ang II axis of RAS.[2]

The potential protective roles of ACE2 in SARS-CoV2 infection and COVID-19 morbidity and mortality have recently been reviewed.[3] Further evidence comes from the vitamin D increasing effect on ACE2 expression recently highlighted by Kumar et al[4] In addition, the inhibitory effect of vitamin D on the pro-inflammatory, pro-oxidant and vasoconstrictive RhoA/Rho kinase (ROCK) pathway[5] also helps, on a mechanistic basis, to comprehend the protective role of vitamin D for COVID-19 prevention. ROCK inhibition increases activity and levels of ACE2 and improves ROCK activity-induced lung injury,[6] further highlighting the importance of increasing ACE2 expression, also *via* vitamin D-induced ROCK inhibition, in SARS-CoV2 target tissues.

Our studies in Bartter's and Gitelman's syndrome patients (rare genetic tubulopathies) to explore and better define the human RAS and RhoA/ROCK systems[7,8] provide further background for the protective effects of increased levels of ACE2 and ROCK inhibition against SARS-CoV2 infection, indirectly supporting the protective effect of vitamin D. These patients have activated RAS and high Ang II levels, yet blunted Ang II-mediated cardiovascular effects and normotension or hypotension. Moreover, they have increased and correlated levels of both ACE2 and Ang 1-7, blunted ROCK activity and activation of anti-inflammatory, anti-proliferative, antioxidant and anti-atherosclerotic defences,[7,9] reproducing the effects induced by vitamin D on ACE2 and ROCK signalling in a human model

of endogenous ACE2-Ang 1-7 axis activation. These data suggest that, in addition to the use of angiotensin receptor blockers and/or ACE inhibitors and/or ROCK inhibitors, vitamin D may also be beneficial to increase ACE2 and reduce ROCK activity. Furthermore, a telephone survey of over 100 of our Gitelman's and Bartter's patients, all of whom were from hotspots of the COVID-19 pandemic in Northern Italy, found none of them infected with COVID-19.[10] This is significant evidence (95% CI 0%-3% compared to the estimated true COVID-19 prevalence in Northern Italy of 8.7%, 95% CI 8.7%-8.8%, $P = 0.004$), that increased ACE2 and reduced ROCK activity may have beneficial effects in COVID-19 prevention and/or treatment.

Given the rapidly evolving nature of the COVID-19 pandemic and in consideration of the reported effects of vitamin D on ACE2 and ROCK, vitamin D might also be used to reduce the severity of COVID-19.

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AUTHORSHIP

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Letter: ciclosporin and vedolizumab for steroid-refractory ulcerative colitis

EDITORS,

We read with interest the recently published article by Ollech et al examining the efficacy and safety of induction therapy with calcineurin inhibitors transitioned to vedolizumab in steroid-refractory ulcerative colitis patients.[1] There is a great need to evaluate possible therapeutic strategies in severe steroid-refractory inflammatory bowel disease that can help to assure colectomy-free survival with acceptable long-term safety profile. Here, we would like to share our experiences on the efficacy and safety of sequential ciclosporin and vedolizumab therapy using a different therapeutic scheme to that reported by the Chicago Inflammatory Bowel Disease Center.