Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Folic acid as placebo in controlled clinical trials of hydroxychloroquine prophylaxis in COVID-19: Is it scientifically justifiable?

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ABSTRACT

Using folic acid (FA) as placebo complicates the interpretation of the findings of few RCTs evaluating safety and efficacy of hydroxychloroquine prophylaxis in COVID-19. FA is found to bind to furin-protease and spike: ACE2 interface of SARS-CoV-2. In clinical studies, FA level was lowest among severe patients compared to mild and moderate disease. A single controlled study reported the benefit of combination of folic acid with Pyridoxine & cyanocobalamin in terms of clinical and laboratory cure parameters. One hypothesis associates the differences in geographical variation of disease severity with prevalence of methyl tertahydrofolic acid reductase (MTHFR) C677T polymorphism. Other possible domains, where FA is hypothesized to be beneficial are COVID-19 associated pulmonary hypertension and hyper-homocystinemia. So, scientific justification of using folic acid as placebo in COVID-19 trials seems scientifically not credible and this may be one of the major factors for failure of many agents. We need to be more careful in choosing our placebo especially when conducting a placebo controlled trial.

Folic acid is being used as placebo in few RTCs of evaluating safety and efficacy of hydroxychloroquine prophylaxis in COVID-19 [1]. However, one issue complicates the interpretation of the findings of these trials. Folic acid is gradually coming up an anti-COVID-19 agent. in a multimodal network-biology based study on SARS-CoV-2 human interactome, folic acid was predicted as a top candidate for drug repurposition (16th rank) [2] as agent for re-purposing against COVID-19. In in-silico studies, folic acid is found to bind to NSP-13 [3], furin [4], spike:ACE2 interface [5,6], PLPro [5], MPro [5] and NSP15 [5] of SARS-CoV-2, which are important targets from drug design perspective.

5,10 methyltetrahydrofolate is converted to 5-methyl-tetrahydrofolate by the enzyme methyl tertahydrofolic acid reductase (MTHFR) and thus helps in providing methyl groups for recycling of homocysteine to methionine. A single study hypothesized that the differences in geographical variation of COVID-19 disease severity may be related to the prevalence of (MTHFR) C677T popymorphism [7]. High dose folic acid is again hypothesized as a potential treatment of pulmonary hypertension (even when associated with COVID-19) and folic acid may help in the same by reversing uncoupling of eNOS and restoring NO production [8].

NSP14 of SARS-CoV is a guanine N7-methyl-transferase and is crucial for viral transmission and replication of SARS-CoV-2 and thus SARS-CoV-2 may use host S-adenosyl methionine (SAM) for viral RNA capping [9], utilization of which results in production of homocysteine, which enhance ACE-2 activation [10] and SARS-CoV-2 may take help of this enhanced activated ACE2 system to get entry to host cell [9]. High homocysteine is reported in the context of severe COVID-19 also or patients with progression of disease [11]. In clinical studies, folic acid is known to lower the level of homocysteine. In COVID-19 also, in a single controlled study, patients treated with Angiovit (Pyridoxine:4mg, folic acid;5mg & cyanocobalamin:6μg) showed reduced duration of fever and hospital stay, and normalized the level of homocysteine, D-Dimer and CRP [12]. In clinical studies, with 162 Israeli patients, Itelman et al found that folic acid level was lowest among severe patients compared to mild and moderate severity category [13].

So, scientific justification of using folic acid as placebo in COVID-19 trials seems scientifically not credible and this may be one of the major factors for failure of an anti COVID-19 agent.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. N Engl J Med 2020;383(6):517–25. https://doi.org/10.1056/NEJMoa2016638.

[2] Gysi DM, Valle ÍD, Zitnik M, Ameli A, Gan X, Varol O, et al. Network Medicine Framework for Identifying Drug Repurposing Opportunities for COVID-19. ArXiv: 200407229 [Cs, q-Bio, Stat] 2020.

Abbreviations: NSP, Non structural protein; MPro, main protease; PL Pro, Papaine-like protease; NO, Nitric oxide; HCQ, Hydroxychloroquine; RCT, Randomized controlled trial; ACE2, Angiotensin converting enzyme 2; eNOS, endothelial nitric acid synthase.

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[3] Ugurel OM, Mutlu O, Sariyer E, Kocer S, Ugurel E, Inci TG, et al. Evaluation of the potency of FDA-approved drugs on wild type and mutant SARS-CoV-2 helicase (Nsp13). Int J Biol Macromol 2020;163:1687–96. https://doi.org/10.1016/j.ijbiomac.2020.09.138.
[4] Sheybani Z, Dokoohaki MH, Negahdaripour M, Dehdashti M, Zolghadr H, Moghadami M, et al. The role of folic acid in the management of respiratory disease caused by COVID-19 2020. doi: 10.26434/chemrxiv.12034980.v1.
[5] In silico virtual screening-based study of nutraceuticals predicts the therapeutic potentials of folic acid and its derivatives against COVID-19 2020. doi: 10.21203/rs.3.rs-31775/v1.
[6] Prajapat M, Shekhar N, Sarma P, Avti P, Singh S, Kaur H, et al. Virtual screening and molecular dynamics study of approved drugs as inhibitors of spike protein S1 domain and ACE2 interaction in SARS-CoV-2. J Mol Graph Model 2020;101:107716. https://doi.org/10.1016/j.jmgm.2020.107716.
[7] Life-threatening course in coronavirus disease 2019 (COVID-19)_ Is there a link to methylenetetrahydrofolic acid reductase (MTHFR) polymorphism and hyperhomocysteinemia? | Elsevier Enhanced Reader n.d. doi: 10.1016/j.mehy.2020.110234.
[8] Wiltshire E, Peña AS, MacKenzie K, Shaw G, Couper J. High dose folic acid is a potential treatment for pulmonary hypertension, including when associated with COVID-19 pneumonia. Med Hypotheses 2020;143:110142. https://doi.org/10.1016/j.mehy.2020.110142.
[9] Singh Y, Gupta G, Kazmi I, Al-Abbasi FA, Negi P, Chellappan DK, et al. SARS CoV-2 aggravates cellular metabolism mediated complications in COVID-19 infection. Dermatologic Therapy n.d.;n/a:e13871. doi: 10.1111/dth.13871.
[10] Li T, Yu B, Liu Z, Li J, Ma M, Wang Y, et al. Homocysteine directly interacts and activates the angiotensin II type I receptor to aggravate vascular injury. Nat Commun 2018;9(1). https://doi.org/10.1038/s41467-017-02401-7.
[11] Yang Z, Shi J, He Z, Lü Y, Xu Q, Ye C, et al. Predictors for imaging progression on chest CT from coronavirus disease 2019 (COVID-19) patients. Aging (Albany NY) 2020;12(7):6037–48.
[12] Boyko AN, Shamalov NA, Boyko OV, Arinina EE, Lyang OV, Dubchenko EA, et al. The first experience with Angiovit in the combination treatment of acute COVID-19 infection. Neurol Neuropsychiatry Psychosomatics 2020;12(3):82–6.
[13] Itelman E, Wasserstrum Y, Segev A, Avaky C, Negru L, Cohen D, et al. Clinical characterization of 162 COVID-19 patients in Israel: preliminary report from a large tertiary center. Isr Med Assoc J 2020;22:271–4.

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