CORRESPONDENCE

Rosuvastatin Myotoxicity After Starting Canagliflozin Treatment

TO THE EDITOR: Brailovski and colleagues (1) attributed their patient’s rosuvastatin-induced myotoxicity to a possible rosuvastatin-canagliflozin interaction. The assumed interaction was based on known and speculated factors. The known factors include the roles of organic anion-transporting polypeptides (OATPs) 1B1 and 1B3 in facilitating rosuvastatin uptake into hepatocytes and breast cancer resistance protein (BCRP) in facilitating its intestinal absorption and biliary/renal elimination. Subsequent speculation was that rosuvastatin accumulation resulted from inhibition of the OATPs and BCRP by canagliflozin. However, this speculation is not supported by the cited study. Canagliflozin had less than 50% in vitro inhibition of OATP1B1 and OATP1B3, and canagliflozin in vivo inhibition of the uptake transporters was determined not to be expected according to basic models. Moreover, canagliflozin was not found to be an inhibitor of BCRP at the highest feasible concentration in the used assay (2).

We believe that the development of rhabdomyolysis in this case was multifactorial and involved patient and drug characteristics. Patients of Asian descent have been shown to have an approximately 2-fold increase in rosuvastatin exposure compared with White patients at similar doses. Hence, a rosuvastatin dosage of 40 mg/d is contraindicated in Asian patients in Canadian prescribing information (3). Furthermore, this patient’s pharmacogenetic testing showed a c421 C>A polymorphism in the ABCG2 gene encoding for BCRP; this could have played a role in this patient’s rosuvastatin-altered pharmacokinetics. The baseline plasma rosuvastatin level at which patients can tolerate this medication varies widely on the basis of clinical and pharmacogenetic predictors (4).

Change in renal function after canagliflozin initiation also should be considered. In the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial, canagliflozin initiation was associated with an initial short-term reduction in estimated glomerular filtration rate (5). This patient’s chronic kidney disease stage (3B) at baseline predisposed her to a decrease in estimated creatinine clearance to less than 30 mL/min/1.73 m² after canagliflozin initiation and a potential 3-fold increase in rosuvastatin exposure. The rosuvastatin dosage should not have exceeded 10 mg/d per dosing recommendations (3). In summary, a more plausible explanation for this patient’s development of rhabdomyolysis is short-term worsening of renal function secondary to canagliflozin initiation in addition to her predisposing factors (that is, Asian descent, receipt of a rosuvastatin dosage of 40 mg/d, advanced age [76 years], and stage 3B chronic kidney disease) that resulted in rosuvastatin accumulation, subsequent rhabdomyolysis, and associated hepatic injury.

Nevertheless, this case remains valuable because it highlights the importance of considering an initial decrease in renal function with canagliflozin, especially in patients with chronic kidney disease. Close monitoring and appropriate dose adjustments are warranted in such patients.

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References
1. Brailovski E, Kim RB, Juurlink D. Rosuvastatin myotoxicity after starting canagliflozin treatment: a case report [Letter]. Ann Intern Med. 2020;173:585-7. doi:10.7326/L20-0549
2. Mamidi RNVS, Dallas S, Sensenhauser C, et al. In vitro and physiologically-based pharmacokinetic based assessment of drug-drug interaction potential of canagliflozin. Br J Clin Pharmacol. 2017;83:1082-96. [PMID: 27862160] doi:10.1111/bcp.13186
3. Product monograph: CRESTOR rosuvastatin calcium tablets, 5, 10, 20 and 40 mg. AstraZeneca Canada; 2020.
4. DeGorter MK, Tirona RG, Schwarz UI, et al. Clinical and pharmacogenetic predictors of circulating atorvastatin and rosuvastatin concentrations in routine clinical care. Circ Cardiovasc Genet. 2013;6:400-8. [PMID: 23876492] doi:10.1161/CIRCGENETICS.113.000899
5. Perkovic V, Jardine MJ, Neal B, et al; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380:2295-306. [PMID: 30990260] doi:10.1056/NEJMoa1811744

TO THE EDITOR: Brailovski and colleagues (1) report the first drug-drug interaction (DDI) between canagliflozin and a statin. However, no myotoxicity signal was seen in the clinical development program (which consisted of >19 000 participants receiving canagliflozin) or during postmarketing use (which totaled more than 4.9 million patient-years of exposure). This program included the long-term CREDENCE study in patients with type 2 diabetes and stage 2 to 3 chronic kidney disease and the CANVAS (CANAgliflozin cardioVascular Assessment Study) Program in patients with type 2 diabetes at high cardiovascular risk, both with approximately 70% concomitant statin use (>9% received rosuvastatin; data on file). No imbalance in the incidence of rhabdomyolysis or other relevant adverse events was observed in these placebo-controlled trials.

In Brailovski and colleagues’ case report, the patient had several confounding factors, including Asian race, stage 3B chronic kidney disease, and hypothyroidism. Each of these is labeled as a contraindication for rosuvastatin, 40 mg/d, because of the risk for rhabdomyolysis.

Furthermore, the clinical course of this patient’s chronic kidney disease and her plasma rosuvastatin concentration before canagliflozin treatment were not available, confounding the causality assessment. The authors noted a more than 15-fold increase in the plasma rosuvastatin concentration at admission compared with that of a historical control group (composed of a White population). However, they did not consider the effect of the patient’s Asian race, heterozygous BCRP phenotype, concomitant medications, and estimated glomerular filtration rate of approximately 30 mL/min/1.73 m², all of which would probably predispose her to higher rosuvastatin concentrations (2).

The authors propose a DDI mechanism involving inhibition of uptake (OATP1B1 and OATP1B3) and efflux (BCRP) transporters. A dedicated DDI study with canagliflozin and
rosuvastatin was not conducted. However, canagliflozin, 300 mg/d, did not show clinically relevant in vitro inhibition of OATP1B1, OATP1B3, or OAT3 or a clinical DDI with simvastatin (OATP1B1/ 
cytochrome P450 3A4 substrate) (3). In addition, canagliflozin has shown no in vitro inhibition of BCRP up to the maximum feasible concentration (that is, 16 μmol/L) (3). The more than 15-fold increase in plasma rosuvastatin concentration reported by Brailovski and colleagues is much higher than both the maximum observed effect (approximately 2-fold) mediated by intestinal BCRP inhibition with a potent BCRP inhibitor (fostamatinib) (4) and the combined inhibitory effect of OATP1B1, OATP1B3, and BCRP (≤11-fold) observed with such potent inhibitors as cyclosporine and rifampicin (5). Finally, the normalization in amino- 
transferase concentrations after the patient’s rhabdomyolysis resolved suggests that these elevated values could have been caused by muscle injury rather than being hepatic in origin.

In conclusion, although this case report highlights an interesting clinical finding, it fails to definitively establish a DDI between canagliflozin and rosuvastatin because of the patient’s confounding conditions and the limited availability of information. Additional investigations may be needed.

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References
1. Brailovski E, Kim RB, Juurlink D. Rosuvastatin myotoxicity after starting canagliflozin treatment: a case report [Letter]. Ann Intern Med. 2020;173:585-7. doi:10.7326/L20-0549
2. Birmingham BK, Bujac SR, Elsby R, et al. Rosuvastatin pharmacokinetics and pharmacogenetics in Caucasian and Asian subjects residing in the United States. Eur J Clin Pharmacol. 2015;71:329-40. [PMID: 25630984]
doi:10.1007/s00228-014-1800-0
3. Mamidi RNVS, Dallas S, Sensenhauser C, et al. In vitro and physiologically-based pharmacokinetic based assessment of drug-drug interaction potential of canagliflozin. Br J Clin Pharmacol. 2017;83:1082-96. [PMID: 27862160]
doi:10.1111/bcp.13186
4. Elsby R, Martin P, Sunry D, et al. Solitary inhibition of the breast cancer resistance protein efflux transporter results in a clinically significant drug-drug interaction with rosuvastatin by causing up to a 2-fold increase in statin exposure. Drug Metab Dispos. 2016;44:398-408. [PMID: 26700956]
doi:10.1124/dmd.115.066795
5. Puerksaranont T, Chu X, Evers R, et al. Pitavastatin is a more sensitive and selective organic anion-transporting polypeptide 1B clinical probe than rosuvastatin. Br J Clin Pharmacol. 2014;78:587-98. [PMID: 24617605]
doi:10.1111/bcp.12377

IN RESPONSE: Dr. Alamer and colleagues rightly note that patients of Asian descent are more prone to rosuvastatin toxicity. Our patient’s loss-of-function polymorphism in the gene encoding for BCRP would have been expected to impart greater rosuvastatin exposure for a given dose (1). However, it does not explain her clinical course, because she had tolerated the same dosage (40 mg/d) for more than 5 years without difficulty. The modest decline in renal function similarly does not explain her presentation, because rosuvastatin clearance is mediated primarily by the liver, with most of the drug recovered in feces and only approximately 10% in urine (2).

Dr. Mamidi and associates assert that hypothyroidism and stage 3B chronic kidney disease are contraindications to a rosu-

vastatin dosage of 40 mg/d. Setting aside the minor role of the kidneys in the elimination of rosuvastatin and the observation that our patient’s hypothyroidism was treated, her myopathic symptoms developed only after initiating canagliflozin despite long-standing renal disease and her receipt of an unchanged dosage of rosuvastatin for many years. If her acute kidney injury at the time of presentation resulted from a canagliflozin-mediated reduction in glomerular filtration (rather than, for example, pigment nephropathy caused by myoglobin), any contribution of this to rosuvastatin accumulation is simply another mecha-

nism by which canagliflozin might alter the pharmacokinetics of rosuvastatin.

Finally, the possibility that our patient’s aminotransferase level elevations reflected skeletal muscle injury rather than liver injury is lessened considerably by the observation that her aspartate and alanine aminotransferase values were similar (1126 U/L and 1017 U/L, respectively). In patients with rhabdomyolysis, aspartate aminotransferase concentrations are typically much higher than alanine aminotransferase concentrations (3).

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References
1. Hua WJ, Hua WX, Fang HJ. The role of OATP1B1 and BCRP in pharma-

cokinetics and DDI of novel statins. Cardiovasc Ther. 2012;30.e234-41. [PMID:
21884024] doi:10.1111/j.1755-5922.2011.00290.x
2. Martin PD, Warwick MJ, Dane AL, et al. Metabolism, excretion, and pharma-

cokinetics of rosuvastatin in healthy adult male volunteers. Clin Ther. 2003;25:2822-35. [PMID: 14693307]
3. Weibrecht K, Dayno M, Darling C, et al. Liver aminotransferases are ele-

vated with rhabdomyolysis in the absence of significant liver injury. J Med

Toxicol. 2010;6:294-300. [PMID: 20407858] doi:10.1007/s13181-010-0075-9

Hydroxychloroquine in Nonhospitalized Adults With Early

COVID-19

TO THE EDITOR: We read Skipper and colleagues’ article (1) with interest but disagree with some of their conclusions, which we believe could not be made from the data shown. Supplement Table 3 concerns medication adherence. It states that in the hydroxychloroquine (HCQ) group, 157 patients received 100% of the tablets; 8 patients received 75% to 99% of the tablets; 16 patients received fewer than 75% of the tablets; and 22 patients never started medication. These values sum to

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203 patients. In the placebo group, the number of patients \((166 + 3 + 12 + 13, \text{respectively})\) sums to 194.

Supplement Table 2 analyzes symptom severity according to medication adherence. It states that in the HCQ group, 165 patients took more than 75% of the tablets (15 to 19 tablets) and 38 patients took fewer than 75% of the tablets (1 to 14 tablets); these values sum to 203 patients. In the placebo group, the number of patients \((169 + 25, \text{respectively})\) sums to 194.

When these 2 tables are compared, it becomes clear that if in Supplement Table 2 less than 75% adherence in fact indicates 1 to 14 tablets, 22 patients should be missing from the HCQ group and 13 patients from the placebo group—the latter of whom never started medication (that is, they received 0 tablets). Because they are not missing, the HCQ group in both tables includes 203 patients and the placebo group 194 patients. As such, we assume that the authors included patients who never started medication in the HCQ and placebo groups.

The issue is not whether the authors should have stated “0-14 tablets” or “1-14 tablets” but is instead a matter of excluding patients who did not start treatment from the intention-to-treat analysis. The designation “1-14 tablets” induces the reader to assume that the authors performed the usual analysis, excluding patients who did not start treatment. Even in intention-to-treat analysis, if no treatment was applied, the usual procedure is to exclude these patients from the full analysis set (www.clinfo.eu/itt-vs-pp).

We acknowledge that ignoring those patients who stopped treatment because of adverse effects introduces biases. However, that does not apply to this situation, because these 22 patients who never started HCQ treatment never experienced any adverse effects and 13 patients never started the placebo regimen; they did not start treatment for reasons not related to group allocation. No biases might arise from excluding patients who never started treatment being allocated to both the HCQ and placebo groups. However, keeping them in the full analysis set might mask any positive effects of HCQ. Masking the positive effects of a drug during a pandemic is a harmful choice.

If a medication were found to work under optimal conditions in the trial setting, adherence to this medication in the field would be far better. The uncertainty about the efficacy of a drug being tested in the trial setting may mean that trial participants are less likely to persevere with unpleasant adverse effects of treatment than those who have been assured of the efficacy of their treatment (2). Yet, the authors seem to disregard their own positive results for HCQ found when patients taking more than 75% of the tablets are considered, namely, a significant 19.5% relative benefit in symptom severity (2-tailed \(P = 0.022\)).

In the Supplement, the authors “caution against overinterpretation of this result,” a 19.5% relative benefit in symptom severity, and contend that “this [adherent HCQ] group did not improve any more than the non-adherent hydroxychloroquine group nor the non-adherent placebo group.” However, unlike the comparison between the treated and untreated groups, that between the adherent and nonadherent groups is invalid. In this case, the latter groups are not selected by randomization and are subject to “nonadherence bias”—that is, nonadherent patients might not have taken the drug because, for example, they were healthier than adherent patients. This is corroborated by the data in Supplement Table 2, which show that the small nonadherent group did much better overall than the larger adherent group.

We understand that the proper way to evaluate the data is to do both an analysis of the intention-to-treat population (excluding, as usual, patients who took 0 tablets) and a per protocol analysis of the patients with 75% adherence to the treatment. The consequence of these considerations is that such conclusions as “hydroxychloroquine did not substantially reduce symptom severity in outpatients with early, mild COVID-19” as cited in the abstract and Discussion section cannot be assumed when a possible positive effect might arise from the rightful exclusion of patients who never started treatment and there is a clear 19.5% beneficial effect of HCQ over placebo when patients who took the tablets are compared (that is, a per protocol analysis).

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References
1. Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19. A randomized trial. Ann Intern Med. 2020;173:623-31. doi:10.7326/M20-4207.
2. Dodd S, White IR, Williamson P. Nonadherence to treatment protocol in published randomised controlled trials: a review. Trials. 2012;13:84. [PMID: 22709676] doi:10.1186/1745-6215-13-84

TO THE EDITOR: We read Skipper and colleagues’ article (1) about the use of HCQ for the treatment of outpatients with early coronavirus disease 2019 (COVID-19)-compatible symptoms or a confirmed diagnosis of COVID-19 with interest. Despite the absence of a statistically significant difference in any of the selected outcomes, the negative results of this study must be interpreted with caution. At first, the authors established as a primary outcome an ordinal scale of disease severity (not hospitalized, hospitalized, intensive care unit stay, or death). The evaluation was influenced by the lower-than-expected incidence of hospitalizations that after interim analysis required the primary outcome to change. Another relevant issue is that the study was originally scaled to find a 50% reduction in those outcomes, which seems overly optimistic.

The HCQ group surprisingly had a 50% lower incidence of a composite outcome for hospitalization and death for any cause (reported \(P = 0.29\)). Patients treated with HCQ made up 24% of those with persistent COVID-19-compatible symptoms at 14 days versus 30% of the placebo group, denoting a nonsignificant absolute reduction of 20% between groups (\(P = 0.21\)). If confirmed in adequately dimensioned trials, this difference is clinically meaningful. The new primary outcome (that is, mean reduction from baseline in a 10-point visual analogue scale for disease severity) at day 14 was close to 1.0 point in the placebo group, indicating lack of relevance of that end point in practice at the time of follow-up. Nevertheless, at 10 days of randomization (11 to 14 days after the start of symptoms), there was a 0.42-point absolute reduction in the visual analogue scale (\(P = 0.050\)).

Use of HCQ in patients with COVID-19 has a low a priori belief of clinical benefit because of unavailable translational evidence, lack of benefit in previous research with other viruses, and no benefit in previous adequately performed observational research and randomized controlled trials (2, 3). The absolute results reported must be considered with caution and interpreted within the limits of the CI for

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Use of HCQ in patients with COVID-19 has a low a priori belief of clinical benefit because of unavailable translational evidence, lack of benefit in previous research with other viruses, and no benefit in previous adequately performed observational research and randomized controlled trials (2, 3). The absolute results reported must be considered with caution and interpreted within the limits of the CI for
all outcomes. The results of Skipper and colleagues’ study naturally do not support the use of HCQ in early COVID-19. However, their findings offer insight for future research in such specific populations and do not prove a lack of any clinically relevant benefit.

References
1. Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19: A randomized trial. Ann Intern Med. 2020;173:623-31. doi:10.7326/M20-4207
2. Schluger NW. The saga of hydroxychloroquine and COVID-19: a cautionary tale [Editorial]. Ann Intern Med. 2020;173:662-3. doi:10.7326/M20-5061
3. Boulware DR, Pullen MF, Bangdiwala AS, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for COVID-19. N Engl J Med. 2020;383:517-25. [PMID: 32492293] doi:10.1056/NEJMoa2016384

IN RESPONSE: To address Drs. Paiva and Tausk, the protocol and statistical analysis plan called for an intention-to-treat analysis whereby everyone randomly assigned was analyzed. A modified intention-to-treat analysis similar to our results when we excluded those who did not start therapy with the study medicine and the relatively small percentage of patients who received open-label HCQ (n = 1), as well as those who stopped therapy before the study end date. In this randomized, double-blind trial, less than 10% of patients who received HCQ versus 7.8% (15 of 194) of patients without symptoms at 14 days is 16 persons (95% CI, 3-65 [benefit] persons). The original intention-to-treat analysis reported that 24.4% of patients who received HCQ versus 30.4% of patients who received placebo had symptoms at day 14.

A per protocol analysis is generally recognized as being biased, because it ignores those who stop medication because of adverse effects. In this randomized, double-blind trial, less than 100% adherence (range, 5% to 89%) was achieved more frequently with HCQ (11.8% [24 of 203] of patients) than with placebo (7.8% [15 of 194] of patients), often because of medication adverse effects or spontaneous improvement. As Supplement Table 2 presents, those with less than 75% adherence—which includes those who never started the medicine—had greater resolution of symptom severity. Yet, when restricting the analysis to those with 100% adherence as a per protocol analysis, ongoing symptoms existed at day 5 in 54.1% (85 of 157) of patients who received HCQ versus 56.6% (94 of 166) of patients who received placebo. At day 14, a total of 25.2% (39 of 155) of the HCQ group had ongoing symptoms.

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doi:10.7326/L21-0001

References
1. Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19: A randomized trial. Ann Intern Med. 2020;173:623-31. doi:10.7326/M20-4207
2. Sheybani Z, Dokoohaki MH, Negahdaripour M, et al. The role of folic acid in the management of respiratory disease caused by COVID-19. ChemRxiv. Preprint posted online 30 March 2020. doi:10.26434/chemxiv.12034980.v1
3. Itelman E, Wasserstrum Y, Segev A, 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. [PMID: 32378815]
4. Acosta-Elias J, Espinosa-Tanguma R. The folate concentration and/or folic acid metabolites in plasma as factor for COVID-19 infection. Front Pharmacol. 2020;11:1062. [PMID: 32765270] doi:10.3389/fphar.2020.01062
5. Boyko AN, Shamalov NA, Boyko OV, et al. The first experience with Angiovit in the combination treatment of acute COVID-19 infection. Neurolgy, Neuropsychiatry, Psychosomatics. 2020;12:82-6. doi:10.14412 /2074-2711-2020-3-82-86
Thus, neither a modified intention-to-treat nor a per protocol analysis substantially differs from the original intention-to-treat analysis.

In response to Dr. Araujo, we did not find a statistical difference in COVID-related hospitalizations or death with HCQ (2.2% [5 of 231] of patients) versus placebo (3.4% [8 of 234] of patients). Two non-COVID events took place in the placebo group that required hospital observations of less than 24 hours. Adjudication occurred while investigators were blinded. In a similar early outpatient treatment randomized trial (n = 293), Mitjà and colleagues found no virologic effect of HCQ (0.07 log_{10} copies/mL higher at 7 days with HCQ) compared with no therapy (1). Their incidence of all-cause hospitalization was 5.9% (8 of 136 patients) with HCQ versus 7.0% (11 of 157 patients) with standard of care in Catalonia (1). A second large randomized trial by Omrani and associates (n = 456) (2) similarly reported no virologic effect of either HCQ alone or HCQ with azithromycin, nor did they find any reduction in hospitalization with HCQ (2.0% [3 of 152 patients]), HCQ and azithromycin (2.6% [4 of 152 patients]), or placebo (2.6% [4 of 152 patients]). A third large randomized trial in Brazil was halted because of futility, with no effect on hospitalization or death (risk ratio, 1.00 [95% CI, 0.45 to 2.21]) (3). An ongoing effort is pursuing this by pooling data across 8 outpatient randomized trials.

We note to Dr. Bhattacharyya and coworkers that the data on whether folic acid has activity against severe acute respiratory syndrome coronavirus 2 in humans to prevent or mitigate COVID-19 are underwhelming. Although interesting, in silico studies are low-quality evidence. In pregnant women, Acosta-Elias and Espinosa-Tanguma reported a 0.95-fold risk for COVID-19-related hospitalization, which is decreased relative to influenza (4). However, the Centers for Disease Control and Prevention reported that pregnant women were 2- to 3-fold more likely to require an intensive care unit stay, invasive ventilation support, or extracorporeal membrane oxygenation (5) despite being a population that commonly receives prenatal folate supplementation. The referenced 50-person case-control study involved a different population of hospitalized pregnant women than the current study and used substantially higher 150-mg total dose of folic acid versus the 7.6 mg given in our trial (6). When we compared symptom severity by placebo composition, the mean visual analogue scale score did not differ at day 5 (mean score of 2.1 [SD, 2.5] for folic acid vs. 2.5 [SD, 2.7] for lactose; P = 0.51) or at days 10 (P = 0.27) or 14 (P = 0.76). Further, Mitjà and colleagues, who used no placebo, reported similar overall results (1). As the available data currently stand, we believe placebo remains valid. Effective early outpatient therapy to prevent disease progression is important; among repurposed oral medicines, fluvoxamine seems more promising than HCQ or folic acid (7).

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References
1. Mitjà O, Corbacho-Monné M, Ubals M, et al; BCN PEP-CoV-2 Research Group. Hydroxychloroquine for early treatment of adults with mild COVID-19: a randomized-controlled trial. Clin Infect Dis. 2020. [PMID: 32674126] doi:10.1093/cid/ciaa1009
2. Omrani AS, Pathan SA, Thomas SA, et al. Randomized double-blinded placebo-controlled trial of hydroxychloroquine with or without azithromycin for virologic cure of non-severe COVID-19. EClinicalMedicine. 2020; 29:100645. [PMID: 33251500] doi:10.1016/j.eclinm.2020.100645
3. Lee Z, Rayner CR, Forrest JI, et al. The rise and fall of hydroxychloroquine for the treatment and prevention of COVID-19. Am J Trop Med Hyg. 2021;104:35-B. [PMID: 32336703] doi:10.4269/ajtmh.20-1320
4. Acosta-Elias J, Espinosa-Tanguma R. The folate concentration and/or folic acid metabolites in plasma as factor for COVID-19 infection. Front Pharmacol. 2020;11:1062. [PMID: 32765270] doi:10.3389/fphar.2020.01062
5. Zambrano LD, Ellington S, Strid P, et al; CDC COVID-19 Response Pregnancy and Infant Linked Outcomes Team. Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status—United States, January 22-October 3, 2020. MMWR Morb Mortal Wkly Rep. 2020;69:1641-7. [PMID: 33151921] doi:10.15585/mmwr.mm6944e3
6. Boyko AN, Shamalov NA, Boyko OV, et al. The first experience with Angiovit in the combination treatment of acute COVID-19 infection. Neurology, Neuropsychiatry, Psychosomatics. 2020;12:82-6. doi:10.14412/2074-2711-2020-3-82-86
7. Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. JAMA. 2020;324:2292-300. [PMID: 33180097] doi:10.1001/jama.2020.22760