



# Favipiravir and the Need for Early Ambulatory Treatment of COVID-19

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The commentary by McCullough emphasizes the urgent need for early ambulatory therapy of coronavirus (CoV) disease 2019 (COVID-19) (1). Unfortunately, no treatment has been proven to prevent disease progression and hospitalization. Although dismissed by McCullough as only a “theoretical” gold standard, randomized controlled trials (RCTs) are absolutely necessary for COVID-19, which in most cases is self-limiting. Despite the challenges of a pandemic, large RCTs, such as RECOVERY (2), have been completed and provided important evidence to guide treatment of COVID-19.

The treatment algorithm suggested by McCullough including “immediate” commencement of zinc and  $\geq 2$  “antivirals” (hydroxychloroquine [HCQ] with azithromycin [AZ] or doxycycline) or favipiravir alone is not evidence based (3). Inhibition of severe acute respiratory syndrome (SARS)-CoV-2 *in vitro* or in animal or human studies has not been demonstrated for doxycycline or zinc (4). In a meta-analysis, HCQ was not associated with reduced mortality, and HCQ plus AZ significantly increased mortality in hospitalized patients (5). Observational studies of hospitalized patients with reduced mortality associated with HCQ with and without AZ had significant confounders (e.g., corticosteroid use) (6). RCTs using HCQ with and without AZ have not demonstrated virological or clinical benefit for prophylaxis or outpatient treatment of COVID-19 (7, 8). Preclinical evidence does not support the use of HCQ for COVID-19. Although HCQ inhibited SARS-CoV-2 in simple *in vitro* cell culture systems, HCQ did not demonstrate anti-SARS-CoV-2 activity (with or without AZ) in human airway epithelium or in macaque models (9). HCQ lacked activity in SARS-CoV-2-infected hamsters, “thus providing no scientific basis for its further use in COVID-19” (10).

Favipiravir had *in vitro* activity (11) and potent antiviral activity at high doses in a SARS-CoV-2 hamster model (10). In a nonrandomized clinical study, favipiravir was associated with shorter times to SARS-CoV-2 clearance (12). In an RCT in hospitalized patients, favipiravir was associated with a high rate of viral clearance on day 5 of illness (13). In an open-label randomized trial in patients with mild disease, favipiravir did not significantly improve viral clearance by day 6 but was associated with a reduced time to defervescence (14). Further RCTs in ambulatory patients (15) should provide further data on antiviral activity and possible benefit on outcome.

The other nonantimicrobial treatments included in the proposed algorithm are also not supported by evidence. The RECOVERY trial established that dexamethasone was associated with reduced mortality for patients receiving invasive mechanical ventilation or supplemental oxygen but not for patients receiving no respiratory support at randomization (2). The safety and efficacy of corticosteroids in early disease has not been proven and cannot be recommended. Colchicine was associated with improved times to clinical deterioration in an open-label randomized clinical trial (16).

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However, confirmation of benefits in large, long-term studies is required prior to including colchicine in treatment algorithms (17). Although thromboembolism is a well-recognized complication, the efficacy or safety of directly acting oral anticoagulant therapy for COVID-19 is not proven and cannot be recommended.

McCullough's fervent advocacy for attention to early ambulatory treatments of COVID-19 must be commended. This enthusiasm should be channeled into further RCTs to generate evidence of safety and efficacy of proposed treatments which may "turn the tide" against this deadly pandemic.

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