Research Article

HCQS in RECOVERY Trial: The Context is Divergent from the Community Scenario

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Abstract

The RECOVERY Collaborative Group in a trial by the same name concluded that hospitalized Covid-19 patients who received HCQS did not have a lower incidence of death at 28 days than those who received usual care. This trial has led to a paradigm shift in the perception of HCQS in the management of COVID-19. We do a critical appraisal of the RECOVERY trial and express our point of view on the relevance of HCQS in the management of COVID-19. We also reveal the flaws in the RECOVERY trial that may have led to poor outcomes with HCQS and try to keep the debate alive regarding its therapeutic benefit.

***Keywords**: Hydroxychloroquine, Coronavirus, Trial, Randomised.*

RECOVERY (Randomized Evaluation of COVID-19 Therapy) is an adaptive, platform trial that investigated multiple treatments, in hospitalized COVID-19 patients in the United Kingdom (UK). **(**1**)** Patient enrolled in the RECOVERY trial were randomized to standard care or to one of six treatment arms: hydroxychloroquine (HCQS), dexamethasone, lopinavir-ritonavir, azithromycin, convalescent

plasma, and, in second randomization for patients who deteriorate, to tocilizumab.1542 patients were randomized to hydroxychloroquine (HCQS) and 3132 patients randomized to usual care, with mortality at day 28 as the primary outcome. Secondary outcomes were the time until discharge from the hospital and initiation of mechanical ventilation (MV)/ death (among patients not on MV at the time of randomization). The death rate in covid-19 patients who took HCQS was 25.7% compared with 23.5% in patients provided with only usual hospital care (P = 0.10). This difference was not statistically significant. Patients in the HCQS group had a longer duration of hospitalization than those in the usual-care group (median, 16 days vs. 13 days) and a lower probability of discharge alive within 28 days (59.6% vs. 62.9%). Among the patients who were not undergoing MV at baseline, the number of patients who had progression to MV/ death was higher among those in the HCQS group compared to usual hospital care (30.7% vs 26.9%). The investigators concluded that HCQS didn't improve 28-day mortality, duration of hospital stay, or risk of progressing to MV/ death in hospitalized COVID-19 patients. **(**2**)**
A critical appraisal of the trial reveals several study weaknesses that limit the interpretation of the HCQS arm.

In the study, the severity distribution of mild cases is 23.2%, moderate to severe is 60.1% and critically ill is 10.7%, whereas the usual distribution of severity of mild cases is 81%, moderate to severe cases is 14% and critically ill is 5% in community **(**3,4**)**. The severity distribution of the disease in the HCQS arm in the trial was skewed with a higher proportion of severe/ critically ill. The higher all-cause mortality in the HCQS arm may also be attributable to the higher proportion of the elderly population in that arm compared to the usual care arm (37.4% vs. 32.5% for ≥70 to <80 years and 45.2% vs. 41.3% for ≥80 years). The elderly have rapidly progressive clinical deterioration and more susceptible to adverse clinical outcomes. **(**5**)** Poor baseline group characteristics in form of predominantly more severe patients and more elderly population led to worse outcomes in the HCQS arm.

Million et al in their retrospective analysis of 1061 SARS-CoV-2 positive hospitalized patients of whom most had the mild disease (95%), found HCQS with Azithromycin led to a low proportion with worsening of disease (ICU transfer,0.9% and mortality, 0.75%) and only 4.4% patients had persistent viral shedding on day 10 **(**6**)**. Lagier et al in their retrospective study of 3737 COVID-19 patients, treated with HCQS /Azithromycin and other regimens found that HCQS with Azithromycin was associated with a decreased risk of transfer to ICU / death, decreased risk of hospitalization ≥10 days and shorter duration of viral shedding. **(**7**)**

SARS-CoV-2 viral loads are associated with disease progression and increased risk of death. **(**8**)** Meta-analysis by Million et al reveals that chloroquine derivatives (HCQS or chloroquine) improved clinical

and virological outcomes and reduced mortality. **(**9**)** HCQS is effective when administered early in the disease course in outpatients and showed efficacy in the majority of the studies in early inpatients (within 48 hours of admission). **(**10**)** Thus, the optimal window for therapeutic intervention with HCQS is early in the course of infection and before severe inflammatory reaction ensues. **(**11**)** In the RECOVERY trial, the median time between symptoms onset and randomization and HCQS administration was 9 days and a substantial proportion of patients (16.7%) were already on mechanical ventilation. The study was neither designed, nor power, to study the impact of HCQS on the early disease.

The Government of India guidelines mandates total HCQS dose of 2400 mg whereas the RECOVERY trial administered 8800 mg, which might have been responsible for the higher incidence of cardiac arrhythmia and cardiac cause of mortality in the HCQS arm. **(**1,12**)** HCQS had no excess risk of serious adverse effects, in the short term when used alone and in standard doses (in approximately a million patients). **(**13**)** Overreactions to cardiotoxicity case reports and observational data have been allowed to impede the conduct of the randomized controlled trials needed to provide robust evidence on risks and benefits. **(**14**)**

Due to the overtly high dose of HCQS and the delay in initiating treatment with it and the fact that the vast majority of patients had already progressed to the late stage of the disease, the RECOVERY trial seems flawed.

Up to 20% of symptomatic individuals will progress to severe or critical disease. While treatment options for patients with severe disease are hospitalization and corticosteroids (treatment of choice for critically ill patients), treatments that can be administered early during the course of infection to prevent disease progression are urgently needed. **(**15, 16**)**. Remdesivir requires daily infusions for up to 10 days and is not suitable for an ambulatory setting. **(**17**)** Dexamethasone has not been tested in early, mild disease, and its immune-suppressive effects could potentially worsen clinical outcomes in this setting. Due to the lack of implementation of large-scale vaccination or SARS-CoV-2 specific therapies, the use of repurposed antiviral drugs like HCQS remains the only valid practical consideration. **(**18**)**

The risk-benefit calculus in mild to moderate disease differs from that of severe disease. **(**19**)** It's unjustified that the purported lack of benefit of HCQS in hospitalized patients is extrapolated to lack of any therapeutic benefit in non-severe patients. HCQS treatment for patients with the mild disease is safe with few adverse effects, easy to administer, low cost and scalable. The politicization of HCQS is a sad indictment of society's polarized discussion but rationally we must scrutinize "evidence" with subtlety and refinement. For a country like India, with a large population, considering its minimal risk

and favorable safety profile, cost-effectiveness, availability, and affordability, the use of HCQS in the fight against COVID-19 appears rationale. **(**20**)** Effective outpatient treatment options for early COVID-19 deserve the full support of the medical community and the public.

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