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Research

Assessing the efficacy and safety of hydroxychloroquine as outpatient treatment of COVID-19: a randomized controlled trial

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Abstract

Background: Identification of therapies to prevent severe COVID-19 remains a priority. We sought to determine whether hydroxychloroquine treatment for outpatients with SARS-CoV-2 infection could prevent hospitalization, mechanical ventilation or death.

Methods: This randomized controlled trial was conducted in Alberta during the first wave of the COVID-19 pandemic without direct contact with participants. Community-dwelling individuals with confirmed SARS-CoV-2 infection (by reverse transcription polymerase chain reaction [RT-PCR] viral ribonucleic acid test) within the previous 4 days, and symptom onset within the previous 12 days, were randomly assigned to oral hydroxychloroquine or matching placebo for 5 days. Enrolment began Apr. 15, 2020. The primary outcome was the composite of hospitalization, invasive mechanical ventilation or death within 30 days. Secondary outcomes included symptom duration and disposition at 30 days. Safety outcomes, such as serious adverse events and mortality, were also ascertained. Outcomes were determined by telephone follow-up and administrative data.

Results: Among 4919 individuals with a positive RT-PCR test, 148 (10.2% of a planned 1446 patients) were randomly assigned, 111 to hydroxychloroquine and 37 to placebo. Of the 148 participants, 24 (16.2%) did not start the study drug. Four participants in the hydroxychloroquine group met the primary outcome (4 hospitalizations, 0 mechanical ventilation, 4 survived to 30 days) and none in the placebo group. Hydroxychloroquine did not reduce symptom duration (hazard ratio 0.77, 95% confidence interval 0.49–1.21). Recruitment was paused on May 22, 2020, when a since-retracted publication raised concerns about the safety of hydroxychloroquine for hospitalized patients with COVID-19. Although we had not identified concerns in a safety review, enrolment was slower than expected among those eligible for the study, and cases within the community were decreasing. Recruitment goals were deemed to be unattainable and the trial was not resumed, resulting in a study underpowered to assess the effect of treatment with hydroxychloroquine and safety.

Interpretation: There was no evidence that hydroxychloroquine reduced symptom duration or prevented severe outcomes among outpatients with proven COVID-19, but the early termination of our study meant that it was underpowered. **Trial registration:** ClinicalTrials.gov, no. NCT04329611

Eighteen years ago, the severe acute respiratory syndrome (SARS) experience[1–5] highlighted limited knowledge of early treatments for novel pandemic respiratory viruses. With the emergence of SARS-CoV-2, early experience in Wuhan,[6] the Lombardy region of Italy[7,8] and New York City[9] demonstrated the need to suppress severe disease to prevent health system collapse. Hydroxychloroquine, derived from the centuries-old antimalarial medicine quinine, has broad antiviral effects and immunomodulatory properties, making it an attractive candidate to be repurposed for SARS-CoV-2 infection. The precise mechanisms of immunomodulation are uncertain, but the net result is inhibition of macrophage production of pro-inflammatory cytokines tumor necrosis factor (TNF)–α and

Competing interests: See the end of the article.

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interleukin (IL)–6.[10] Hydroxychloroquine was explored as a putative agent for SARS in 2003, but that epidemic was contained before it could be adequately tested. In vitro effects on SARS-CoV-2 and enthusiasm from preliminary clinical investigations in COVID-19 resulted in its rapid, widespread, off-label use worldwide.[11–16]

We began a randomized placebo-controlled trial, leveraging the entire Alberta public health system infrastructure, to assess whether early hydroxychloroquine treatment in outpatients with SARS-CoV-2 infection would prevent progression to severe disease requiring hospitalization or mechanical ventilation, or resulting in death.

Methods

Study design and setting

This investigator-initiated, randomized, double-blind, placebo-controlled trial was conducted in Alberta, with enrolment beginning Apr. 15, 2020. Alberta has a population of 4.4 million, of whom about two-thirds live in urban settings. The protocol is available in Appendices 1, 2 and 3, available at www.cmajopen.ca/content/9/2/E693/suppl/DC1. An independent data and safety monitoring committee provided study oversight.

The trial was designed to determine whether early hydroxychloroquine treatment in community-dwelling individuals infected with SARS-CoV-2 prevented progression to severe disease. The publicly funded health system in Alberta is singularly responsible for testing, reporting and providing health services to all residents, permitting all individuals with confirmed SARS-CoV-2 infection to be identified. Alberta Health Services (AHS) staff obtained permission to share contact information with researchers after results of reverse transcription polymerase chain reaction (RT-PCR) tests were disclosed to infected individuals. Research coordinators then telephoned individuals who consented to be contacted and discussed the study, conducted screening, obtained informed consent and randomly assigned eligible participants by telephone.

To limit risk to study personnel and enable province-wide participation, all study interactions were conducted by telephone (including obtaining informed consent) or email. Screening was supported by access to the participants' provincial electronic health record, discussion with a study physician (as needed), and a telephone language translation service used during the calls. Calls, including the consent discussion, were recorded for quality assurance.

Participants

Adults with SARS-CoV-2 infection confirmed by RT-PCR from a nasopharyngeal or pharyngeal swab within the previous 4 days, with symptom onset within the previous 12 days and with at least 1 risk factor for severe disease (Appendix 1, Table S1) were eligible. Those who were hospitalized, pregnant or breastfeeding, unable to swallow pills or unable to comply with the medical regimen, or had used hydroxychloroquine, chloroquine, lumefantrine, mefloquine or quinine within the previous 30 days were excluded. Those at higher risk for arrhythmia secondary to hydroxychloroquine, including those concurrently using a drug that prolonged the corrected QT interval (QTc) and those with a modified Tisdale Risk Score of 7 or greater (Appendix 1, Table S2), were excluded.

We anticipated that enrolment could be completed between April and September 2020 given the rate of SARS-CoV-2 infection, as we expected up to half of infected patients would participate.

Intervention

The hydroxychloroquine dose was 800 mg orally in divided doses on day 1 followed by 200 mg twice daily for 4 days, or identical matching placebo (12 tablets over 5 days). The study drug was delivered to participants' homes anywhere in the province by courier. Treatment initiation was confirmed by telephone or email.

Outcomes

The primary outcome was development of severe disease defined as the composite of hospitalization, invasive mechanical ventilation, or death within 30 days. Secondary outcomes included 1) days to COVID-19 recovery (symptom duration), defined as the number of days from randomization to symptom resolution; 2) disposition at 30 days, defined as recovered, ongoing symptoms but not hospitalized, hospitalized or deceased; and the proportion of participants 3) deceased, 4) admitted to ICU and 5) hospitalized, within 30 days. Safety outcomes were the proportion of participants with serious adverse events and the proportion with emesis.

Data sources

The primary outcome was obtained from administrative data, including vital statistics, hospital admission dates, intensive care admission and hospital discharge summaries. The Alberta electronic medical record includes Alberta Netcare, which encompasses all hospitalizations, diagnostic test results and outpatient pharmacy prescriptions. In addition, the routine administrative data from the Discharge Abstract Database, the provincial vital statistics registry and the National Ambulatory Care Reporting System were used.

Telephone interviews at 7 and 30 days, supported by review of electronic medical records, determined adherence, adverse events, disposition at 30 days, symptom duration and care during hospitalizations. Only serious adverse events and the predetermined adverse event of new or worsening emesis — considered because of the potential effect on adherence — were collected.

Randomization and blinding

Randomization was conducted using a custom-developed online tool to allow for dynamic randomization and allocation concealment. We used a minimal sufficient balance randomization tool to ensure balance on age, sex, risk status (binary variable based on age and other identified risks), days since symptom onset and provincial health zone (5 categories).[17] Participants were randomly assigned

to receive either hydroxychloroquine or placebo in a stochastically governed (not blocked) 2:1 ratio. We chose the 2:1 ratio to encourage participation by allocating a greater chance of receiving the active agent. Masking to allocation sequence was complete because randomization assignment was determined dynamically at randomization. All participants and the research team were blinded except for the research pharmacist and randomization website programmer.

Statistical analysis

The absolute effect size was estimated based on the Italian experience, assuming that up to 20% of the Alberta population (4.4 million) could acquire SARS-CoV-2 infection (n = 840 000), that 16% of those infected (n = 134 400) could require hospitalization and that 3% of those infected (n = 25 200) could require invasive mechanical ventilation. We estimated the risk of severe disease to be at least twice as high in high-risk populations, so low-risk individuals were excluded. Assuming a 16% rate of the primary outcome, a risk ratio of 0.65, with 2:1 randomization and 85% power, we estimated that 1446 evaluable patients with complete follow-up were required (n = 482 placebo; n = 964 active treatment).

Comparisons were conducted under a superiority framework with a 2-sided level of 0.05. Secondary analyses followed a prespecified protected hierarchy; adjustments were not made for multiplicity. Treatment effects were reported with 95% confidence intervals (CIs). The intention-to-treat (ITT) population included all randomized participants. The per-protocol population included participants who were adherent to the treatment, defined as taking 10 or more of 12 tablets. The safety population consisted of participants who took any study drug.

We compared the proportion of participants in each treatment group who reached the primary outcome using the Fisher exact test. Although analysis of symptom recovery originally stipulated a semi-competing risks model with a competing risk of death, this was not required as no deaths were observed. Days to symptom recovery was plotted using Kaplan–Meier curves, and a log-rank test was used to test the hypothesis that the recovery-free curves did not differ between treatment and placebo. We estimated hazard ratios for treatment from a Cox proportional hazard regression model. The proportional hazards assumption was assessed graphically and through statistical testing.[18] We tested the proportion of participants with safety outcomes using the Fisher exact test.

For assessing symptom duration, participants who recovered before randomization or were asymptomatic were removed, as were those without follow-up at day 7 or day 30 whose symptoms at randomization were unconfirmed. Participants without recovery dates were censored at their last follow-up with a known disposition. When disposition was known only at randomization, participants were considered lost to follow-up for this outcome and censored at day 1.

We used the statistical software SAS (SAS Institute Inc.) and R (R Core Team). Study data were collected and managed using REDCap electronic data capture tools hosted and supported by the Women and Children's Health Research Institute at the University of Alberta.[19]

Ethics approval

The trial was approved by health research ethics committees of the University of Calgary and the University of Alberta, and all participants provided informed consent.

Results

During the study period, 4919 individuals with a positive PCR test for SARS-CoV-2 were identified (Figure 1), and 1207 consented to being contacted. A total of 233 participants were screened, and 148 were randomized, 111 to hydroxychloroquine and 37 to placebo (Figures 1 and 2). Participant characteristics are provided in Table 1. Telephone translation services were required by 10.6% of those contacted and 8.1% of randomized participants (Appendix 1, Table S3).

Before starting treatment, 11 of 148 (7.4%) of randomly assigned participants withdrew. Five participants discontinued treatment on investigator recommendation. Figure 2 shows adherence to treatment and to telephone follow-up. Administrative data collection was complete for 147 of 148 participants.

Recruitment was paused on May 22, 2020, when a since-retracted publication[20,21] raised concerns about the safety of hydroxychloroquine for hospitalized patients with COVID-19. A safety review was triggered, and 5 patients taking the study drug were asked to discontinue. Although no safety concerns had been identified in our study, enrolment was slower than expected among those eligible for the study, and cases within the community were decreasing. Recruitment goals were deemed to be unattainable during this wave of infection, and the trial was not resumed.

Outcomes

In the ITT population, 4 of 147 (2.7%) participants met the primary outcome (Table 2). All 4 were hospitalized, none required mechanical ventilation and all survived to 30 days. All 4 were randomized to hydroxychloroquine, but 1 never started treatment and 2 discontinued early. The difference between groups for the primary outcome was not significant (risk difference 3.6%, 95% CI 0.1%–7.1%) whether the missing outcome from 1 participant was considered as meeting the end point or not, or if the analysis included only participants who took at least 1 dose of the study drug (data not shown).

Symptom duration from enrolment was assessed for 124 of 148 participants (Table 2). There was no evidence suggesting nonproportional hazards (p = 0.3), and the estimated hazard of symptom recovery for hydroxychloroquine was nonsignificant at 0.77 (95% CI 0.49–1.21) compared with placebo (Figure 3). Other secondary outcomes in the ITT population are shown in Table 2. Results in the per-protocol population did not meaningfully differ (Appendix 1, Table S4).

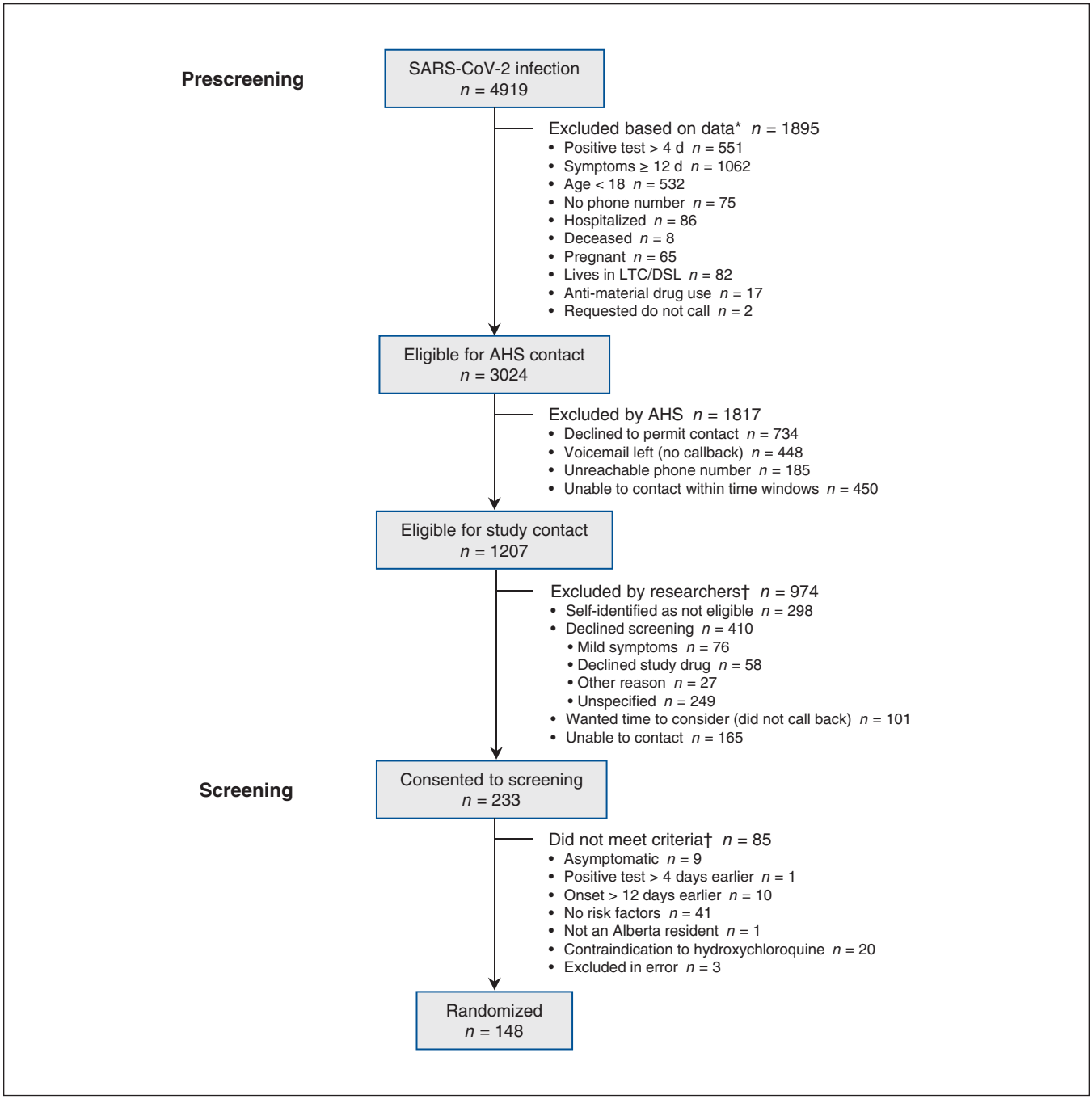

Figure 1: Screening process. Note: AHS = Alberta Health Services, DSL = designated supportive living, LTC = long-term care. *Reasons are not mutually exclusive. †Assigned to the first exclusion identified.

Although all safety events occurred in participants randomized to hydroxychloroquine, after pausing the trial, the data and safety monitoring committee reviewed unblinded data and identified no safety concerns. None of the 4 hospitalizations (Table 3), all for COVID-19 pneumonia, were judged to be related to treatment. One participant discontinued treatment after taking 2 tablets and was hospitalized 13 days after randomization. Another participant took 5 tablets, but emesis that was present before enrolment prevented starting the drug, and this participant was hospitalized 3 days after randomization. A third participant was hospitalized 1 day after randomization; treatment was completed in hospital. Five participants reported new or worsening emesis after initiating the study drug. One completed the study drug; 4 discontinued treatment within 3 days.

Interpretation

The trial recruited only 10% of the target sample size, stopping early because of a report on hydroxychloroquine safety

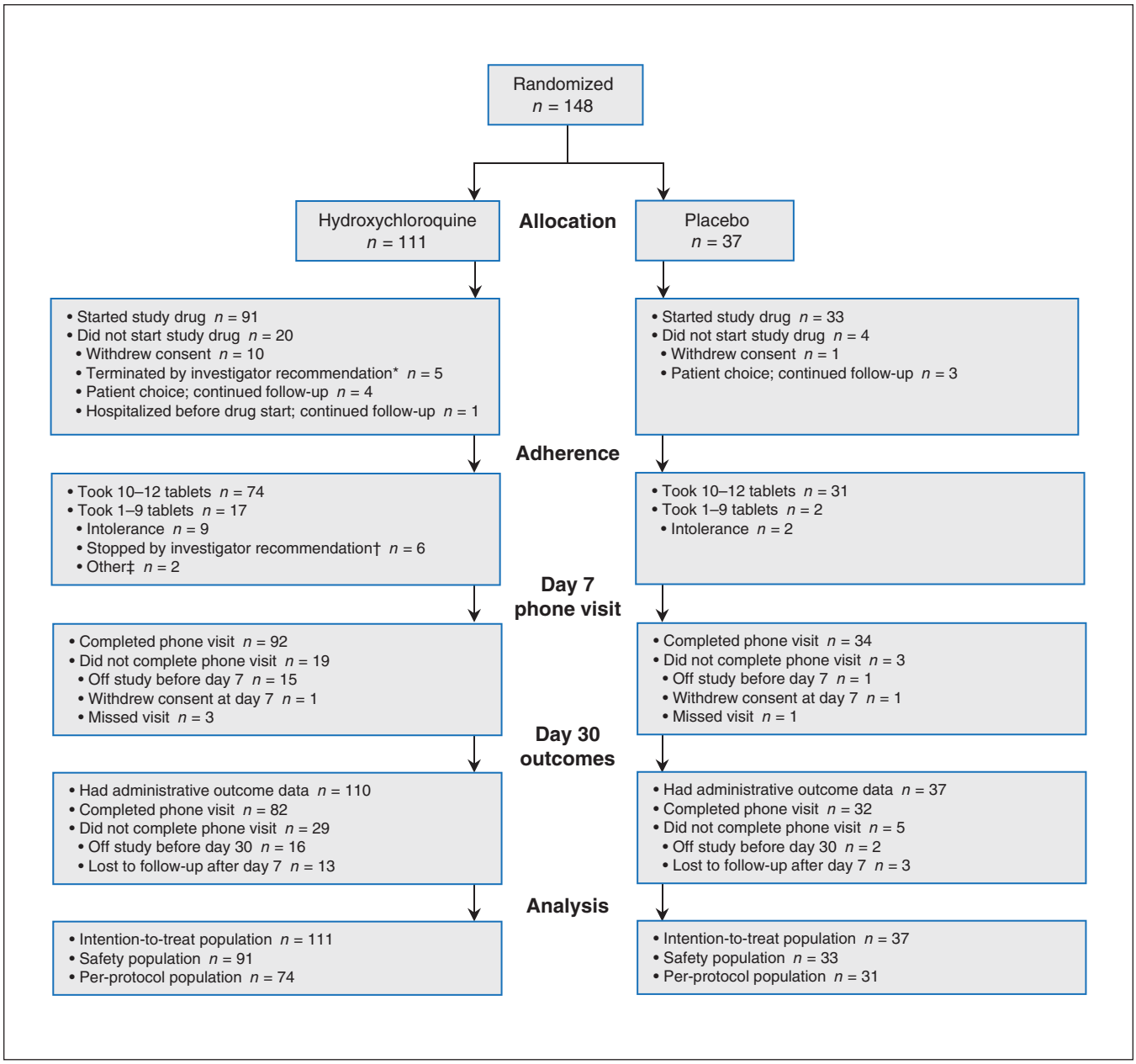

Figure 2: Consort diagram. *Five participants did not meet eligibility criteria: 3 had no risk factors for severe COVID-19 and 2 were taking a contraindicated medication. †One participant did not meet eligibility criteria (asymptomatic) and 5 participants were stopped for safety signal. ‡Two participants stopped study drug owing to COVID-19 symptoms that started before randomization.

(that was subsequently retracted)[20,21] and a rapid decline in disease prevalence coinciding with control of the first wave of the COVID-19 pandemic. There was neither a signal of treatment effect nor any safety signal observed, but the early termination of our study meant that it was underpowered. The lack of any early signal in our data is concordant with recently published results.[22–33]

The prevalence of the primary outcome was nonsignificantly lower than initially estimated, with trial participants having a lower nominal rate of hospitalization (2.7%) than the broader Alberta population (4.5%, 266/5878 during the same period) (data provided by Alberta Health). Individuals with COVID-19 from long-term care facilities, where a high infection prevalence and mortality occurred but a higher safety risk was present, were not eligible for enrolment.

The choice to study hydroxychloroquine without adequate preclinical and early human data to estimate an effect size was a known risk that we accepted because of the public health urgency. Studies suggesting early efficacy of hydroxychloroquine for COVID-19 were biased by selection.[11–14] Although initial in vitro studies suggested hydroxychloroquine was effective in inhibiting SARS-CoV-2,[34,35] this was later refuted by studies that tested activity in more appropriate cell lines and animal models.[36–38]

Table 1 (part 1 of 2): Baseline characteristics of participants randomized to hydroxychloroquine or placebo (*n* = 148)

Characteristic	No. (%) of participants*	
	Hydroxychloroquine *n* = 111	Placebo *n* = 37
Age at randomization, yr, mean ± SD	46.7 ± 11.5	46.9 ± 11.0
Sex, female	46 (41.4)	20 (54.1)
BMI, mean ± SD	28.3 ± 7.3	29.0 ± 8.7
Risk status†		
Low	41 (38.0)	12 (32.4)
High	67 (62.0)	25 (67.6)
Common risk factors (present in > 10%)		
Age ≥ 40 yr	91 (82.0)	29 (78.4)
Hypertension (receiving medical treatment)	29 (26.1)	12 (32.4)
Diabetes (taking a hypoglycemic or insulin)	18 (16.2)	11 (29.7)
Asthma (as per physician diagnosis)	12 (10.8)	8 (21.6)
Current cigarette smoker	16 (14.4)	5 (13.5)
Days from symptom onset to randomization,‡ median (IQR)	7 (5–8)	6 (6–9)
Symptoms of COVID-19 since onset‡		
Fever (≥ 37.5°C if measured)	54 (49.1)	20 (54.1)
Cough	81 (73.6)	31 (83.8)
Shortness of breath (dyspnea)	27 (24.5)	13 (35.1)
Chest tightness	35 (31.8)	10 (27.0)
Generally feeling unwell (malaise)	72 (65.5)	28 (75.7)
Sore throat	49 (44.5)	20 (54.1)
Muscle aches or pains (myalgias)	59 (53.6)	26 (70.3)
Head cold or runny nose (coryza)	58 (52.7)	25 (67.6)
Decreased sense of taste or smell (dysgeusia)	60 (54.5)	29 (78.4)
Nausea	39 (35.5)	8 (21.6)
Diarrhea	35 (31.8)	20 (54.1)

Table 1 (part 2 of 2): Baseline characteristics of participants randomized to hydroxychloroquine or placebo (*n* = 148)

Characteristic	No. (%) of participants*	
	Hydroxychloroquine *n* = 111	Placebo *n* = 37
Provincial health zone		
North Zone	1 (0.9)	0
Edmonton Zone	4 (3.6)	0
Central Zone	1 (0.9)	0
Calgary Zone	84 (75.7)	35 (94.6)
South Zone	21 (18.9)	2 (5.4)
Reported race/ethnicity§		
White	36 (32.4)	15 (41.7)
Black	12 (10.8)	0
Asian	53 (47.7)	19 (52.8)
Other	10 (9.0)	2 (5.6)

Note: BMI = body mass index, IQR = interquartile range, SD = standard deviation.
*Unless stated otherwise.
†Risk status missing for 3 participants in the hydroxychloroquine group (no risk factors). Low risk defined as age 40–64 with no other risk factors. High risk defined as age 18–64 with another risk factor, or age ≥ 65 regardless of other risk factors.
‡Excludes 1 participant in the hydroxychloroquine group who was asymptomatic.
§Missing for 1 participant in the placebo group.

For this trial, multiple new processes were rapidly developed and implemented. The challenges of identifying eligible participants in the community, procuring required technology and privacy access for coordinators to work remotely from home, scheduling coordinators, physicians, and AHS staff to work 7 days per week, obtaining verbal consent, the frequent need for language translation, arranging study drug delivery to remote areas 7 days per week, and monitoring adherence were evident early. Despite Alberta's aggressive testing program, individuals often did not get tested early during their illness. When test results were reported, 22% (1062/4919) were already out of the eligibility window. Under Alberta's *Health Information Act*, AHS, as the health data custodian, had to obtain permission from individuals to be contacted by the researchers, which caused an unavoidable delay. Only 40% (1207/3024) agreed to be contacted. Language barriers were another challenge. The largest provincial outbreaks were in 2 meat-packing plants, where many workers spoke neither English nor French.

In our study, commonly reported reasons for declining enrolment were that the prospective participants did not feel sick enough or their symptoms were improving, they did not want to take medication, or they were worried about adverse effects. We speculate that other reasons included a lack of understanding of clinical research, no prior relationship with the researchers, and fear of treatment risk in the setting of a novel disease. These factors likely also contributed to the high proportion who never initiated treatment. Although remote enrolment was necessary owing to the short course of the illness and the requirement to protect study personnel from infection, it was difficult to recruit participants without face-to-face interaction or involvement of a care provider with whom they had a relationship.

An unforeseen external event that hampered this trial was the politicization of hydroxychloroquine. Widespread media attention resulted in polarizing views of the drug. The publication (and retraction owing to unverifiable data) of a large registry study[20,21] that suggested unacceptable

Table 2: Primary and secondary outcomes in the intention-to-treat population (*n* = 148)

Outcome	No. (%) of participants*		
	Hydroxychloroquine *n* = 111	Placebo *n* = 37	*p* value
Primary outcome†‡	4 (3.6)	0	0.6¶
Secondary outcomes			
Time to COVID-19 recovery, d, median (95% CI)§	14 (10–20)	12 (7–18)	0.3**
Disposition at 30 d‡			NC
Recovered	67 (60.9)	29 (78.4)	
Ongoing symptoms, not hospitalized	23 (20.9)	6 (16.2)	
Unknown, not hospitalized or deceased	20 (18.2)	2 (5.4)	
Mortality within 30 d	0	0	NC
Admission to ICU within 30 d‡	1 (0.9)	0	NC
Hospitalization within 30 d‡	4 (3.6)	0	NC

Note: CI = confidence interval, ICU = intensive care unit, NC = secondary outcomes were not compared between groups following the prespecified protected hierarchy.
*Unless stated otherwise.
†Primary outcome: hospitalization, invasive mechanical ventilation or death within 30 days of randomization.
‡Missing for 1 participant in the hydroxychloroquine group who declined consent for data collection after they withdrew from the study. This participant was confirmed to be alive beyond 30 days when contacted for re-consent.
§Includes 89 participants in the hydroxychloroquine group and 35 in the placebo group with data on symptoms duration. Participants who recovered before randomization or were asymptomatic (1 was enrolled in error) were removed, as were 12 without follow-up at day 7 or day 30 whose symptoms at randomization were unconfirmed.
¶Two-sided Fisher exact test.
**Log-rank test.

risk of harm from hydroxychloroquine was a pivotal event. In the context of this negative public perception of hydroxychloroquine, emerging data from other randomized trials of hydroxychloroquine, the low and falling disease prevalence, recruitment challenges, and the realization that the target sample size was unattainable, the trial was permanently halted.

Despite setbacks, there were positive lessons that emerged. Enthusiastic participation from researchers donating their time and expertise, and rapid turnaround for study approval at Health Canada and at institutional ethics boards, and for funding decisions, were remarkable. Health Canada and Alberta research ethics boards embraced innovation to permit verbal-only consent documented by recording. Consortium-based funding and in-kind support came from the entire Alberta research community. Nationally, there were other trials addressing the same question and, in retrospect, more may have been achieved from better coordination at the national level.

Strengths of this study include the successful leverage of Alberta's integrated publicly funded health care system, widespread collaboration of researchers across 2 universities, and successful inclusion of non–English- or French-speaking individuals who are often excluded from trial participation. The study was a real-world example of a registry-based randomized controlled trial using centralized AHS data and involving AHS personnel in telephoning prospective participants. The contactless nature of the trial allowed enrolment throughout the province beyond the major referral centres.

Limitations

Although use of remote technology facilitated province-wide recruitment, it conversely resulted in inefficient recruitment and adherence. A similar approach was used in another trial assessing fluvoxamine for COVID-19.[39] Inclusion of individuals' own primary care physicians may have improved recruitment, enhanced follow-up and accelerated knowledge translation. Provincial data systems could be enhanced by inclusion of a consent registry, or consent might have been obtainable at the time of testing, to avoid the need to obtain consent for research contact in the midst of a crisis. Including a research perspective into emergency preparedness planning could support the development of research strategies that would benefit crises resolution. Because the trial was terminated early, it was

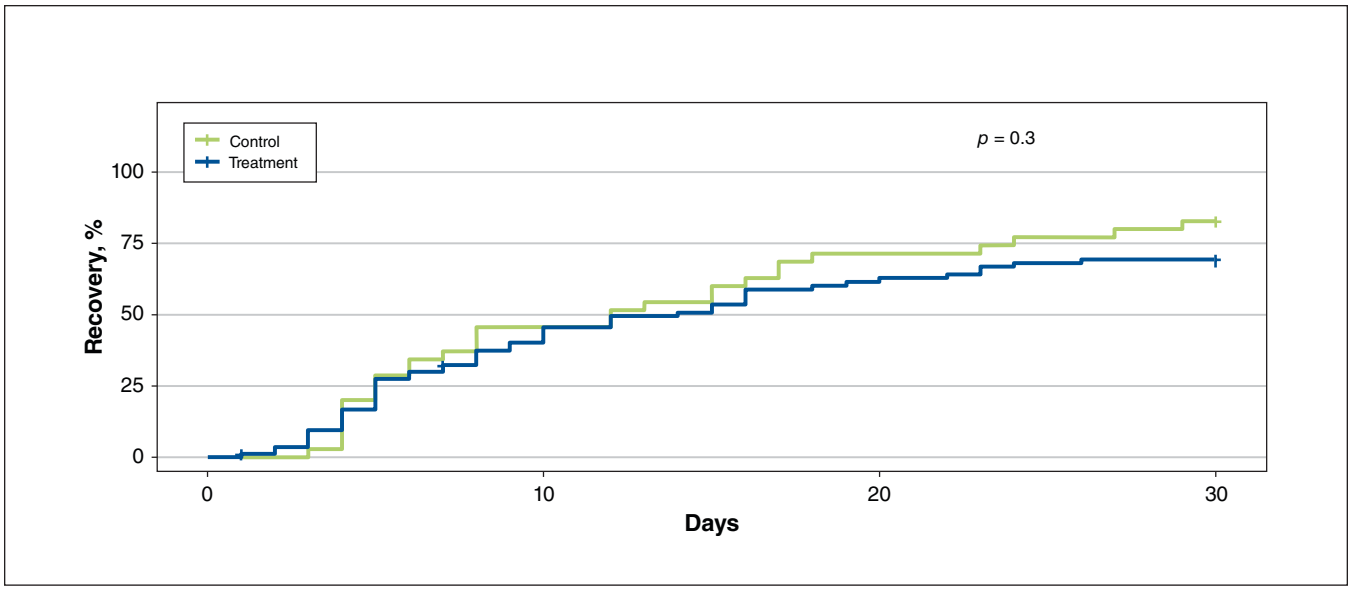

Figure 3: Participants who reached the outcome of symptom resolution over the course of 30 days after randomization in the intention-to-treat population (n = 124). The curves show the cumulative percentage of participants with symptom resolution over the course of 30 days after randomization. Estimates of the cumulative percentage recovered were calculated using Kaplan–Meier survival analysis. Participants were excluded if they recovered on or before randomization (n = 11), were asymptomatic (n = 1), or could not be confirmed symptomatic on randomization and had no follow-up at day 7 or day 30 and symptoms at randomization were unconfirmed (n = 12). Participants without recovery dates were administratively censored at the last follow-up with a known disposition. Participants were censored at day 1 if disposition was unknown at both day 7 and day 30 but they were confirmed to be symptomatic at randomization.

Table 3: Safety outcomes in participants who took at least 1 tablet of the study drug (n = 124)

	No. (%) of participants		
Safety outcome	Hydroxychloroquine n = 91	Placebo n = 33	p value*
SAE within 30 d	3 (3.3)	0	0.6
Emesis within 30 d	5 (5.5)	0	0.3
Mortality within 30 d	0	0	–
Hospitalization within 30 d	3 (3.3)	0	0.6
IMV or death within 30 d	0	0	–

Note: IMV = invasive mechanical ventilation, SAE = serious adverse event.
*Two-sided Fisher exact test.

underpowered, leading to low precision and an inability to draw conclusions about the treatment.

Conclusion

There was no evidence that hydroxychloroquine reduced symptom duration or prevented severe outcomes among outpatients with proven COVID-19, but the early termination of our study meant that it was underpowered. Despite its premature termination, this trial successfully introduced several methodological innovations in the execution of trials in Alberta. While the SARS-CoV-2 vaccines give reason for hope, challenges in production and distribution, vaccine hesitancy, and the emergence of variants mean that the original premise of our study to investigate therapies to prevent severe disease remains real and urgent.

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