ORIGINAL ARTICLE

Early COVID-19 therapy with azithromycin plus nitazoxanide, ivermectin or hydroxychloroquine in outpatient settings significantly improved COVID-19 outcomes compared to known outcomes in untreated patients

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Abstract

In a prospective observational study (pre-AndroCoV Trial), the use of nitazoxanide, ivermectin and hydroxychloroquine demonstrated unexpected improvements in COVID-19 outcomes when compared to untreated patients. The apparent yet likely positive results raised ethical concerns on the employment of further full placebo controlled studies in early-stage COVID-19. The present analysis aimed to elucidate, through a comparative analysis with two control groups, whether full placebo-control randomized clinical trials (RCTs) on early-stage COVID-19 are still ethically acceptable. The Active group (AG) consisted of patients enrolled in the Pre-AndroCoV-Trial (n = 585). Control Group 1 (CG1) consisted of a retrospectively obtained group of untreated patients of the same population (n = 137), and Control Group 2 (CG2) resulted from a precise prediction of clinical outcomes based on a thorough and structured review of indexed articles and official statements. Patients were matched for sex, age, comorbidities and disease severity at baseline. Compared to CG1 and CG2, AG showed reduction of 31.5–36.5% in viral shedding ($p < 0.0001$), 70–85% in disease duration ($p < 0.0001$), and 100% in respiratory complications, hospitalization, mechanical ventilation, deaths and post-COVID manifestations ($p < 0.0001$ for all). For every 1000 confirmed cases for COVID-19, at least 70 hospitalizations, 50 mechanical ventilations and five deaths were prevented. Benefits from the combination of early COVID-19 detection and early pharmacological approaches were consistent and overwhelming when compared to untreated groups, which, together with the well-established safety profile of the drug combinations tested in the Pre-AndroCoV Trial, precluded our study from continuing employing full placebo in early COVID-19.

Keywords: Antiandrogen, clinical equipoise, COVID-19, dutasteride, hydroxychloroquine, ivermectin, nitazoxanide, proxalutamide, SARS-CoV-2, spironolactone

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Background

Coronavirus Disease 2019 (COVID-19) is a highly heterogeneous and multi-systemic infection caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [1] that is particularly harmful to those aged above 60 y/o, with uncontrolled diabetes, hypertension, obesity, androgenetic alopecia (AGA), abuse of anabolic steroids in males and hyperandrogenism in females [2–7].

Effective treatments to improve COVID-19 clinical outcomes, mortality and to prevent post-COVID manifestations are highly desired, while definitive solutions such as effective and safe vaccines are not universally available. Pharmacological interventions during the viral replication stage are likely the best timing to antagonize SARS-CoV-2 infectivity and prevent complications [1,3].

Hydroxychloroquine (HCQ), nitazoxanide (NIT) and ivermectin (IVE), in association with azithromycin (AZI), are popular drugs largely used as off label therapies for early COVID-19. Despite the demonstration of direct or indirect antiviral activity and positive preliminary observations when treatment is

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Abbreviations

5ARi	5alpha-reductase inhibitor
ACEi	Angiotensin converter inhibitors
ADHD	Attention deficiency and hyperactive disorders
AGA	androgenetic alopecia
ARB	Angiotensin-2 receptor blockers
ASA	acetylsalicylic acid
AZI	Azithromycin
BCG	Bacillus Calmette-Guérin
BMO	Body Mass Index
BPH	Benign Prostate Hyperplasia
CCB	Calcium channel blockers
CNS	Central nervous system
CHF	Chronic heart failure
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	infection caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)
DPP4i	Di-peptidyl peptidase 4 inhibitors
GI	Gastrointestinal
GnRH	Gonadotropin-releasing hormone
HCQ	Hydroxychloroquine
IVE	Ivermectin
NSAA	Non-steroidal antiandrogens
NTZ	Nitazoxanide
PCSK9i	Protein convertase subtilisin/kexin type 9 inhibitor
rtPCR	Real time polymerase chain reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SERM	Selective estrogen receptor modulator
SNRI	Serotonin-noradrenaline reuptaker inhibitors
SSRI	Selective serotonin reuptaker inhibitors
SGLT2i	Sodium-glucose co-transporter 2 inhibitors
T2DM	Type 2 diabetes mellitus
URTI	Upper respiratory tract infection
WHO	World Health Organization

started before seven days of symptoms, all of these three drugs – HCQ [8–13], IVE [13–18] and NIT [18–22] lack definitive data regarding their efficacy for COVID-19.

Since the plausibility for their use in COVID-19 is based on their potential antiviral activity, these drugs failed to demonstrate benefits when were tested after the first stage, as expected [16,23], despite a few exceptions [24].

In addition to the above-mentioned drugs, antiandrogens could play a protective action against COVID-19 by the inhibition of transmembrane serine protease 2 (TMPRSS-2) expression, a critical protein that facilitates SARS-CoV-2 viral entry that finds in androgens its only known modulators [3,4,25–32].

Indeed, chronic dutasteride use [28–30] and acute dutasteride [31] and proxalutamide [32] use demonstrated in randomized clinical trials (RCT) to protect against severe COVID-19 in a variety of male populations, which encourages the employment of antiandrogens in further RCTs for early COVID-19.

Our first objective was to compare antiandrogens, HCQ, NIT, IVE and placebo for early COVID-19, based on the assumption that none of these drugs presented actual benefits for any COVID-19 stage (null hypothesis). We first conducted a prospective open-label head-to-head comparison observational study with HCQ, NIT and IVE, with or without antiandrogens, to detect whether any of these drugs would demonstrate superior efficacy and then test the most effective options in double-blind placebo-controlled randomized clinical trials (RCTs), alone and combined with spironolactone (SPIRO), dutasteride (DUTA), or proxalutamide (PROXA) [33–35]. However, during the observational study, the interim analysis demonstrated that while HCQ, NIT and IVE showed similar effects, outcomes were seemingly more effective than those expected for COVID-19. The unexpected, seemingly positive results compelled us to question whether the employment of full placebo-control studies in early-stage COVID-19 would still remain ethically acceptable (Fig. 1).

The objective of the present study was to elucidate whether a full placebo control RCT in early COVID-19 would still be ethically acceptable after the results obtained in the Pre-AndroCoV Trial. To answer this question, we performed independent comparisons with two distinct control-groups, matched for sex, age, comorbidities and disease characteristics, of untreated patients with COVID-19 from the same location as the subjects enrolled in the Pre-AndroCoV Trial and of a control group with the expected outcomes, based on data generated from a thorough and structured review of the literature. With these comparative analyses, we aimed to evaluate whether differences in COVID-19 outcomes actually exist between treated with different regimens and untreated subjects, how different COVID-19 outcomes were, the expected implications of these differences in terms of prevention of hospitalizations, mechanical ventilations, deaths, and post-COVID symptoms and if these discrepancies were sufficient to be considered as irrefutable, leading to mandatory changes in

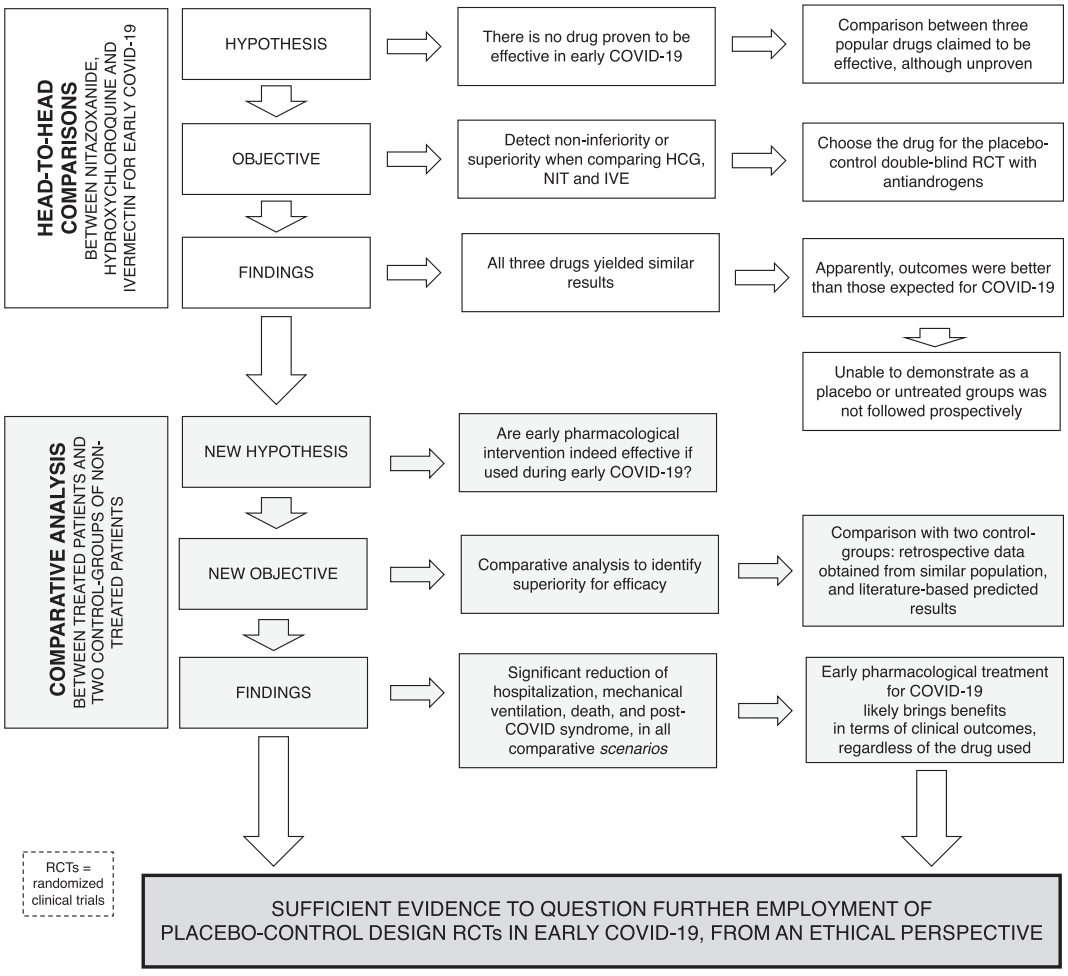

FIG. 1. Rationale for the ethical questioning on the employment of placebo-control design in RCTs for early COVID-19.

the design of further RCTs conducted on early COVID-19, in terms of no longer employing full placebo groups.

Materials and methods

Subject selection

The study was conducted in a single centre (Corpometria Institute, Brasilia, Brazil). Subjects of the Active Group (AG) (n = 585) were confirmed for COVID-19 through an rtPCR-SARS-CoV-2 (Abbott RealTime SARS-CoV-2 Assay, Abbott, USA; or Cobas SARS-CoV-2, Roche, Switzerland), aged 18 y/o and above, with less than seven days of symptoms and 72 hours of diagnosis, and absence of signs of COVID-19 complications. Patients of the AG consented in a formal written form, based on the consent form approved by the Ethics Committee of the National Board Ministry of Health, Brazil (CEP/CONEP: Parecer 4.173.074/CAAE: 34110420.2.0000.0008) that encompasses the use of the drugs of the present analysis.

Two control groups were employed, and both were adjusted for age, sex and presence of comorbidities. Control Group 1 (CG1) (n = 137) was a group of paired untreated patients randomly obtained retrospectively from the population of the same community that had confirmed diagnosis of COVID-19 during the same period of those included in the Pre-AndroCoV Trial, that either refused or did not receive specific treatments for COVID-19, including nitazoxanide, hydroxychloroquine or ivermectin.

A second control group (Control Group 2 - CG2) (paired for 585 patients) resulted from a precise estimative based on a thorough and structured review of articles indexed in PubMed and MEDLINE and statements by official government agencies and specific medical societies [2,36–58], in addition to the living systematic review of the British Medical Journal expected estimates for each outcome in untreated patients [11]. From data obtained, each parameter was estimated for range and median and the least negative data was employed, aiming to underestimate the risks of non-treatment to avoid

overestimation of differences between treatment regimens and lack of treatment. When results had above 20% discrepancy between different sources, the least negative value was employed. When results had differences lower than 20% for the same parameter between studies, the value employed was one standard deviation (SD) below the median in favour of positive outcomes. When a specific parameter had differences above 100%, the range, instead of a specific value, was described (*e.g.*, if the prevalence of a specific symptom was described as being between 10% and 80%, 10%–80% was described, instead of 45%). For these parameters, the least negative value was employed for comparison purposes with AG. The parameters of CG2 were estimated from the proportion between rates for those aged between 40 and 49 y/o with and without comorbidities, assuming a prevalence of comorbidities of 20% (compared to 30% of comorbidities in the AG). For CG2, we avoided statistical analyses from regions with higher case fatality ratios (CFR), like those observed in Northern Italy [69], as this could artificially increase the estimation of the number of preventable complications related to COVID-19.

Selected subjects were characterized for age, sex, the prevalence of obesity, hypertension, type 2 diabetes mellitus, overall comorbidities rate and adjusted accordingly. AG was additionally characterized for the presence of other 35 diseases and 20 drug classes. The medical records of the subjects were recorded individually, medically analyzed in an individual base, while data were compiled into a dataset and deidentified for statistical analysis purposes.

Procedures

A detailed description of the allocation process is described elsewhere [18]. Treatment was optional and all offered drugs that were within standard of care were provided since all early specific pharmacological approaches were based on the literature or as per the Brazilian Government. Drug options were offered in a *quasi*-randomized manner, *i.e.,* options were randomly offered according to specific characteristics, including age, presence and number of comorbidities, number of days of symptoms.

Drugs offered included azithromycin 500mg daily for five days for all patients, in association with one of the following: hydroxychloroquine 400mg daily for five days, nitazoxanide 500mg twice a day for six days, or ivermectin 0.2mg/kg/day in a single daily dose for three days, In addition, repurposed drugs, including dutasteride 0.5mg/day for 15 days and spironolactone 100mg twice a day for 15 days, were optionally offered.

Vitamin D, vitamin C, zinc, apibaxan, rivaroxaban, enoxaparin and glucocorticoids were added according to clinical judgement, the risk for thrombosis and progression of the disease to the inflammatory stage.

Patients that decided to adhere to any treatment were included in the AG. All patients of AG and CG1 groups were followed longitudinally for 90 days for the occurrence of a new-onset or persistence of physical or mental manifestations.

Of the 585 subjects, all patients used azithromycin. A total of 357 patients used NIT, 159 used HCQ and 110 patients used IVE, alone with azithromycin or in combination with other drugs.

Of the 357 patients that used NIT, 69 used the same in combination with HCQ, 46 used in combination with IVE, 146 used in combination with SPIRO, and 27 males used in combination with DUTA.

Of the 110 patients that used IVE, 22 used in combination with HCQ, 82 used in combination with NIT, 66 used in combination with SPIRO and four males used in combination with DUTA.

Of the 159 patients that used HCQ, 21 used in combination with IVE, 113 used in combination with NIT, 86 used in combination with SPIRO and seven males used in combination with DUTA.

Parameters

Clinical outcomes were measured or directly obtained for AG and CG1 and estimated for CG2, including virologic duration (rtPCR-SARS-CoV-2, Abbott RealTime SARS-CoV-2 Assay, Abbott, USA; or Cobas SARS-CoV-2, Roche, Switzerland), time-to-clinical-remission, including and not including anosmia and ageusia, hospitalization rate, mechanical ventilation, deaths and prevalence of post-COVID syndrome, including mental, physical, or both types of manifestations.

CG1 and CG2 underwent pairwise comparative analysis to evaluate consistency between world data of untreated subjects and data generated from the local untreated population. Only parameters with minimally sufficient data and consisting findings between different studies were included. Amplitude effect – estimated number of preventable outcomes.

Since preliminary data demonstrated that hospitalizations, deaths and post-COVID syndrome were likely prevented in the AG, we calculated estimates for the number of patients that avoided progression to any of these complications with treatment regimens.

Statistical analysis

The sample size was determined based on the assumptions that its estimate for the chi-squared test would require 80% power to detect the difference in proportions at $p = 0.05$, at least 95% of subjects would complete the study, and hospitalization and

death rates being between 3 and 20%, and 0.3 and 2.5%, respectively.

From these assumptions, we calculated a minimum of 45 and 125 patients for each group to detect safety and efficacy differences, respectively. Nonparametric ANOVA (Kruskal-Wallis) with adjusted Dunn's test for pairwise analyses when overall $p < 0.05$, assuming that all parameters were distributed non normally. All statistical tests were performed using XLSTAT version 22.4.1 (Microsoft, USA).

Results

Baseline characteristics are presented in Table 1. The proportion between sex, age and comorbidities were similar between the treated population (AG) and both control group 1 (CG1) and control group 2 (CG2), except for obesity that was estimated to be more prevalent in the expected population (CG2) than in AG and CG1. Hypertension and type 2 diabetes were numerically more prevalent in the treated population, although not statistically significant.

The main clinical outcomes are summarized in Table 2. The percentage of asymptomatic subjects was 6.6% in the AG group, 13.3% in the CG1 group, and estimates vary between 15% and 80% of patients expected to be asymptomatic. The expected control population has estimates statistically significantly higher proportions of asymptomatic patients than the groups that were followed-up (overall $p < 0.0001$).

Duration of viral shedding (Median and 95% confidence interval – 95%CI) was 14 (0.5) days in the treated population, 21 (1.7) days in the untreated population that was followed up, and expected to demonstrate a duration of 20 days in external untreated patients. Duration of SARS-CoV-2 presence was significantly shorter in the treated population ($p < 0.0001$ for both comparisons), with a reduction in viral load between 31.5% and 36.5% compared to the untreated populations.

Time-to-remission of clinical symptoms excluding anosmia and ageusia was (Median – 95%CI) was 5 (0.6) days in treated patients, 18 (2.6) in untreated patients and 19 (3.5) days in the estimated population. COVID-19 clinical duration was significantly lower in treated patients ($p < 0.0001$ versus both untreated groups), with a 70% to 73% reduction in the duration of symptoms.

Time-to-remission of clinical symptoms, including anosmia and ageusia, was (Median – 95%CI) 8 (0.6) days in the AG group, 28 (3.3) days in the CG1 group, and expected to be between 30 and 60 days in the general untreated population. COVID-19 clinical duration, including anosmia, was 70% to 85% lower in treated compared to untreated groups ($p < 0.0001$).

There were no hospitalizations in the treated group, 19.7% of hospitalizations in untreated patients, and an estimate of 7% of hospitalizations in the paired untreated population. Hospitalizations were significantly lower in the untreated versus treated population ($p < 0.0001$ for both comparisons with CG1 and CG2). For every 100,000 people infected with COVID-19, between 14,000 and 19,700 hospitalizations may have been prevented.

While none of the treated patients required mechanical ventilation, 6.6% of the CG1 and 4.9% of the expected for the CG2 group required mechanical ventilation. For every 1000 patients infected with COVID-19, any of the early interventions could prevent between 50 and 66 patients from needing mechanical ventilation.

No treated patients and 1.4% of the CG1 group deceased. In the overall untreated population, a 0.5% mortality rate is expected. When adjusted for larger populations, the mortality

TABLE 1. Baseline characteristics

Baseline characteristics	Treated population (AG) (n = 585)	Control group 1 (CG1) – Untreated population (n = 137)	Control group 2 (CG2) – Expected population characteristics paired for 585 subjects[a]	Overall p-value
Sex				
Male (M)	315 (53.8%)	77 (56.2%)	322 (55%)	n/s
Female (F)	270 (46.2%)	60 (43.4%)	263 (45%)	
Age (y/o)				
Median (95%CI)	42 (0.9)	44 (1.8)	45 (2.0)	n/s
{Min – Max age}	[19-83]	[18–74]	[n/a]	
Hypertension				
Number (%)	105 (17.9%)	22 (16.0%)	80 (13.7%)	n/s
Type 2 diabetes mellitus (T2DM)				
Number (%)	59 (10.1%)	11 (8.0%)	30 (5.1%)	n/s
Obesity				
Number (%)	104 (17.8%)	23 (16.8%)	177 (30.3%) *(p < 0.05 vs treated patients and CG1)*	<0.0001
Overall comorbidities (except obesity)				
Number (%)	151 (25.8%)	26 (21.2%)	117 (20%)	n/s

BMI = body mass index; 95% CI = 95% confidence interval; n/a = non-applicable; n/s = non-significant.
[a]Based on the largest cohorts of COVID-19 patients.

TABLE 2. Clinical outcomes

Clinical outcomes	Treated population (AG) (n = 585)	Control-group 1 (CG1) – Same population controls (n = 137)	Control-group 2 (CG2) – Expected outcomes paired for 585 subjects	Overall p-value	Estimated population protected or level of reduction with treatment (compared to untreated patients)
Asymptomatic *Number (%)*	9 (6.6%)	78 (13.3%) *(p < 0.05 vs treated patients)*	88 to 468 (15 to 80%) (p < 0.05 vs treated population and CG1)	p < 0.0001	n/a
Duration of positive rtPCR (days) *Median (95%CI)*	14 (0.5)	21 (1.7)	20	p < 0.0001	31.5 to 36.5% reduction (in viral shedding duration)
Remission not including anosmia (days) *Median (95%CI)*	5 (0.4)	18 (2.6)	19 (3.5)	p < 0.0001	70 to 73% reduction (in time-to-remission)
Remission including anosmia (days) *Median (95%CI)*	8 (0.6)	28 (3.3)	30 to 60	p < 0.0001	70 to 85% reduction reduction (in time-to-remission)
Brescia COVID-19 Respiratory Severity Scale (0–4) in day 7 *Median (95%CI)*	0 (0)	n/a	1 (1)	p < 0.0001	100% reduction (in respiratory complication)
Hospitalization *Number (%)*	0 (0)	27 (19.7%)	41 (7%)	p < 0.0001	140 to 197 hospitalizations prevented for every 1000 patients treated
Mechanical ventilation *Number (%)*	0 (0)	9 (6.6%)	29 (4.9%) 11,6% (BMJ)	p < 0.0001[a]	50 to 66 mechanical ventilations prevented for every 1000 patients treated
Death *Number (%)*	0 (0)	2 (1.4%)	3 (0.5%) 13% of 5,1%	p < 0.0001[a]	5 to 14 deaths prevented for every 1000 patients treated
Post-COVID Physical symptoms *Number (%)*	6 (1.1%)	42 (30.6%)	322 (55%) 45 to 90%	p < 0.0001	295 to 541 post-COVID physical manifestations prevented for every 1000 patients treated
Post-COVID Mental symptoms *Number (%)*	5 (0.8%)	38 (27.7%)	426 (72.8%)	p < 0.0001	269 to 719 post-COVID mental manifestations prevented for every 1000 patients treated
Post-COVID Overall symptoms *Number (%)*	11 (1.9%)	58 (42.3%)	523 (89.5%)	p < 0.0001	404 to 875 post-COVID syndrome prevented for every 1000 patients treated

BMJ = living systematic review of drugs for COVID-19 in BMJ [11]; n/a = non-applicable.
[a]Adjusted for the impacts on larger populations.

rate would be significantly lower in the treated group, and approximately 5000 to 14,000 deaths are estimated to be prevented for every 1,000,000 cases.

Persisting physical manifestations after COVID-19 was present in 1.1% of treated patients, 30.6% of untreated patients that were followed up, and an estimate of 55% of the overall untreated population may present post-COVID physical manifestations ($p < 0.0001$ for treated versus both groups of untreated populations). For every 1000 infected subjects, between 295 and 541 patients are estimated to be prevented from post-COVID physical manifestations with early pharmacological approaches.

Persisting or new-onset mental symptoms after resolution of COVID-19 are present in 0.8%, 27.7% and expectedly 72.8% of AG, GC1 and GC2, respectively. Treated patients experienced significantly fewer post-COVID mental symptoms than untreated populations ($p < 0.0001$), with an expected reduction of 269 to 719 subjects experiencing post-COVID mental manifestations for every 1000 infected subjects.

The prevalence of post-COVID syndrome was 1.9% in treated patients, 42.3% in untreated patients, and estimated to be up to 89.5% of the population infected. The prevalence was significantly lower in untreated patients than treated groups ($p < 0.0001$). Early treatment is estimated to prevent post-COVID syndrome between 404 and 875 subjects for every 1000 infected subjects.

Discussion

Superiority of early pharmacological interventions for COVID-19: apparent or actual?

When we conducted the observational study comparing HCQ, NIT and IVE, we presumed that there were no actual effective options for early COVID-19, i.e., that none of the drugs would confer any protection. As per the design, we did not include patients that did not undergo any specific treatment since our primary objective was to perform a head-to-head comparison. However, once none of the patients were hospitalized, needed mechanical ventilation, or deceased, questions regarding the superiority of any treatment over none were raised, but could not be answered by the study, as we did not originally include untreated patients, precluding us from any conclusion regarding the overall efficacy. To respond to this question raised by the

clear differences between treated and overall untreated populations, we performed the present comparative analysis based on two different control groups in order to detect reproducibility and consistency between both comparisons. To avoid the potential bias of overestimating our findings, we purposely underestimated risks, complications and negative data of untreated populations and underestimated the benefits of those treated for COVID-19. For the estimation of the CG2, we have considered slightly lower disease duration, hospitalization, mechanical ventilation, death and post-COVID syndrome prevalence than those described by the literature, and we avoided the use of studies that included hospitalized patients and that had median age above 55 y/o. Despite the underestimation of the benefits of our findings and underestimation or risks related to untreated subjects, the present comparative analysis revealed differences unlikely to be random for the most relevant clinical outcomes, including reductions of one-third in viral shedding, two-thirds in clinical duration and the ability to prevent 100% of hospitalizations, mechanical ventilation and deaths, which was consistent across comparisons with CG-1, CG-2 and both. Reduction of deaths and long-term consequences were meaningful when analyzed through a public health perspective. The numbers estimated from the present findings, with at least a moderate level of certainty, that from every 1,000,000 new COVID-19 cases, at least 70,000 hospitalizations, 5000 deaths and 250,000 long-term persistence of symptoms could be prevented with the use of any of the drug combinations presented in this analysis in the seven first days of COVID-19 symptoms. From the perspective of our findings, improvements were found to be dramatic and possibly conclusive when COVID-19 is diagnosed early and one of the three pharmacological options between HCG, IVE and NTZ combined with azithromycin is offered.

While differences were in subjects with a median age below 60 y/o, in subjects above 60 y/o, differences could be more pronounced. Since our study only had fewer than 15% of patients being asymptomatic, the expected CFR for our population was higher than for those obtained through the analysis of seroprevalence.

Our prevalence of comorbidities was higher compared to sex- and age-matched untreated populations, even with lower BMI (when compared to CG2, but no CG1), possibly because we have actively searched for comorbidities that could influence risks in COVID-19. This could have negatively influenced outcomes in the AG, although underdiagnosis of comorbidities in CG2 is possible.

Whether and tol what extent the change in COVID-19 detection towards a more sensitive diagnosis may have affected outcomes in a positive manner is unknown but possible. Correspondingly, a more aggressive approach to the patient suspected for COVID-19 may have been crucial for the better outcomes found in the AG when compared to CGs.

Post-COVID syndrome as an outcome

While mortality plays a key outcome in COVID-19, the notorious presence of persisting symptoms after COVID-19 remission has called attention to the chronic aspects, possibly mediated by the triggering of immunologic maladaptations. Persistent fatigue, brain fog, reduction of cognitive functions, impaired muscle recovery, decreased physical capacity, reduced fertility and sexual function and psychiatric manifestations not fully justified by post-traumatic stress disorder (PTSD), with substantial similarities with Chronic Fatigue Syndrome (CFS) and Burnout syndrome, are among the most commonly described symptoms and may affect up to 85% of patients [59–67]. Because of the potential long-term impairment of life quality, prevention of post-COVID symptoms should be considered as a major endpoint when approaching COVID-19.

In the present study, reductions in the prevalence of post-COVID symptoms in treated compared to untreated populations were greater than differences observed in any other parameter. This finding must be emphasized as an additional benefit that may overcome potential risks of the drug use per se, i.e., even in a hypothetical absence of other benefits, prevention of post-COVID syndrome may alone be sufficient to justify the use of early pharmacological approaches for COVID-19.

The decision of no longer use of placebo in early COVID-19

There is not a specific point from which it becomes ethically questionable to continue a clinical trial [68,69]. However, the fact that a placebo control is necessary to demonstrate efficacy is not sufficient to justify its employment in all circumstances.

While without double-blind placebo-controlled RCTs, it becomes harder to obtain evidence in terms of efficacy profile, from the perspectives of both percentage and an absolute number of patients prevented from complications, the use of safe options that demonstrated preliminary positive data and biological plausibility is highly recommended in the absence of established effective treatments.

The use of repurposed drugs presents several advantages in the context of a public health emergency: 1. The long-term safety profile is well-established, precluding from unexpected adverse effects and drug-related complications; 2. Whenever risks of adverse effects exist, these are known, which allows a directed monitoring and a more precise balancing between benefits and risks; 3. Cost-effectiveness tend to be beneficial due to lower costs of old, non-patented drugs; and 4. General physicians and healthcare providers are familiarized with

already existing drugs, which allows their uses to be not only restricted to specialized centres. This last argument is particularly important in a pandemic with a massive number of new cases, which does not allow all cases to be managed within specialized centres. In the absence of proven therapies, the level of evidence required to recommend the use of drugs known to be safe and inexpensive should not be exceedingly high, at least until further definitive evidence is demonstrated for other drugs that are feasible to be administered in a large scale with accessible cost and sufficient production capacity.

In the case of HCQ, IVE and NIT use for early COVID-19, the prevention of 7%, 5% and 50% to 80% of subjects being hospitalized, intubated and suffering from chronic manifestations, respectively, their well-established safety profile for outpatient use and the social value of early treatment in a pandemic are arguments against the continuation of placebo-controlled studies for early COVID-19. In addition, the estimates for clinical outcomes in COVID-19 are largely based on population studies with positive rtPCR-SARS-CoV-2, not only tested due to symptoms or close contact with infected subjects. This is seen by the large percentage of asymptomatic patients expected for this group. This may underestimate the hospitalization and mortality rates in the estimates of the GC2.

Once hydroxychloroquine, nitazoxanide and ivermectin have been used for a wide range of diseases in the long-term for large populations with favourable cost-effectiveness even when

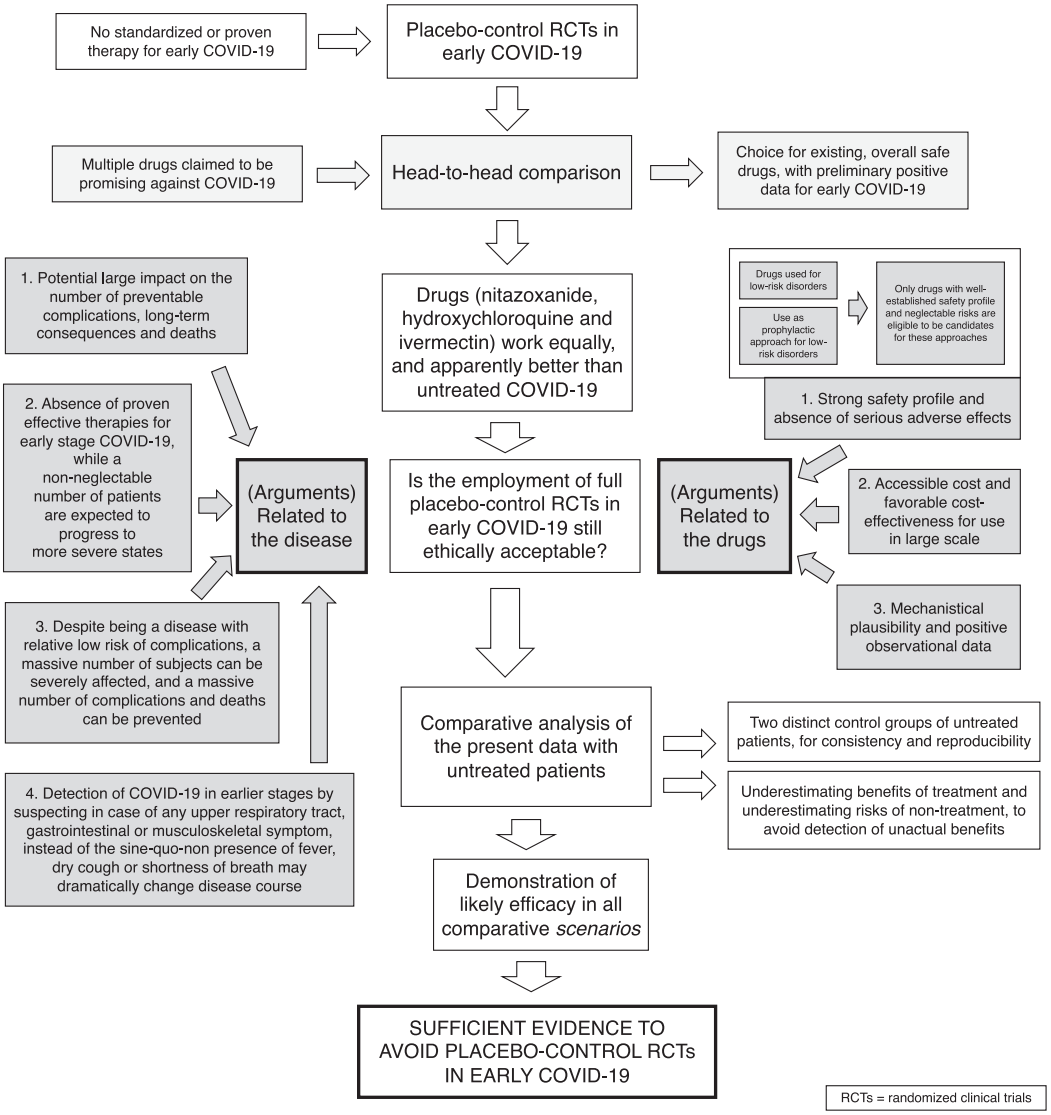

FIG. 2. Ethics in the employment of full placebo-control RCTs in early COVID-19.

used prophylactically, it is intuitive that their use for early COVID-19, when antiviral approaches tend to be more efficient, would be recommended, at least until evidence shows otherwise. Since the development of severe respiratory states can occur very rapidly in COVID-19, the timing to intervention is critical, and early pharmacological approaches showed to be likely efficient to prevent acute respiratory insufficiency.

Because COVID-19 is of public health importance, and the impact of the present findings is likely large, we were no longer ethically allowed to conduct studies with the employment of full placebo, and we found it mandatory to communicate our findings to the overall scientific community. Fig. 2 summarizes the rationale for the conclusions from the present analysis.

Limitations

This is a post-hoc comparative analysis that compared a group of treated patients with a variety of drug combinations with two control groups, one obtained retrospectively and one estimated for the population treated for COVID-19 with several biases, which is only able to offer evidence due to the overwhelming differences.

In particular, drugs that could disclose different results were all combined for comparison purposes. That included hydroxychloroquine, ivermectin and nitazoxanide. Although our previous observational study demonstrated similar outcomes, a formal randomized clinical trial for head-to-head comparisons have not been performed. In addition, all patients received a combination of one of these three drugs and azithromycin. Whether: 1. Azithromycin would work alone; and 2. Combination between hydroxychloroquine, ivermectin and nitazoxanide would yield better results are unknown. However, due to the complex pathophysiology, it is plausible that therapies with different targets against SARS-CoV-2 may present synergistic activity and higher efficacy.

The last but important limitation is that this observational study was conducted during the occurrence of previous viral strains. The novel P.1 Variant of Concern (VOC) that surged in the country where the experiment was conducted, was shown to present higher infectivity, pathogenicity and poorer outcomes, with characteristics that could fulfil criteria to become the first Variant of High Consequence (VOHC) [70]. In this case, multidrug combined therapies tend to be more effective than testing or administering one or two drugs only.

Final discussion

Patients treated with azithromycin combined with nitazoxanide, hydroxychloroquine or ivermectin had significant reductions in virologic and clinical duration, hospitalization, mechanical ventilation, death and post-COVID symptoms, when compared to sex-, age- and comorbidity-matched untreated patients. The well-established safety profile of the drugs used in the present study, the likely benefits presented and the current absence of proven therapies for early COVID-19 bring ethical questions regarding the employment of placebo-control randomized clinical trials in early COVID-19. The medical decision-making on pharmacological interventions is particularly important for patients at high risk of developing severe COVID-19 and in regions where variants, mainly the P.1 variant, is highly prevalent when the natural disease course tends to be worse without pharmacological interventions.

Conclusion

Two-to four-drug treatment regimens for early COVID-19 that obligatorily including AZI, at least one between IVE, NIT and HCG, and optionally DUTA or SPIRO, were demonstrated to be very likely effective for hospitalization, deaths and prevention of post-COVID syndrome, and the use of full placebo for further RCTs on early COVID-19 should be a matter of ethical questioning.

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Transparency declaration

The authors declare no conflict of interest with any of the pharmacological interventions proposed by the present study.

Authorship statement

Dr. Cadegiani was the principal investigator and contributed to the study conception and design, compiled and analyzed the data, and helped write the manuscript. Dr Goren contributed with the study design, analysis of the data, and review of the manuscript. Dr. Wambier performed the statistical analysis, analyzed the data, and helped write the manuscript. Dr. McCoy helped with the study design, helped to analyze the data, and reviewed the last version of the manuscript.

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