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MAJOR ARTICLE

Tenofovir Disoproxil Fumarate/Emtricitabine and Baricitinib for Patients at High Risk of Severe Coronavirus Disease 2019: The PANCOVID Randomized Clinical Trial

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Background. This study was designed to evaluate if patients with high risk for severe coronavirus disease 2019 (COVID-19) would benefit from treatment with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) followed by baricitinib in case of hypoxemia and systemic inflammation.

Methods. PANCOVID is an open-label, double-randomized, phase 3 pragmatic clinical trial including adults with symptomatic COVID-19 with ≥2 comorbidities or aged ≥60 years and was conducted between 10 October 2020 and 23 September 2021. In the first randomization, patients received TDF/FTC or no TDF/FTC. In the second randomization, patients with room air oxygen saturation <95% and at least 1 increased inflammatory biomarker received baricitinib plus dexamethasone or dexamethasone alone. The primary endpoint was 28-day mortality. Main secondary endpoint was 28-day disease progression or critical care unit admission or mortality. The trial was stopped before reaching planned sample size due to the decrease in the number of cases and a mortality rate substantially lower than expected.

Results. Of the 355 included participants, 97% were hospitalized at baseline. Overall, 28-day mortality was 3.1%. The 28-day mortality relative risk (RR) for participants treated with TDF/FTC was 1.76 (95% confidence interval [CI], .52–5.91; $P = .379$); it was 0.42 (95% CI, .11–1.59; $P = .201$) for those treated with baricitinib. The 28-day RR for the main secondary combined endpoint for participants treated with TDF/FTC was 0.95 (95% CI, .66–1.40; $P = .774$); it was 0.90 (95% CI, .61–1.33; $P = .687$) for those treated with baricitinib.

Conclusions. Our results do not suggest a beneficial effect of TDF/FTC; nevertheless, they are compatible with the beneficial effect of baricitinib already established by other clinical trials.

Clinical Trials Registration. EudraCT: 2020-001156-18.

Keywords. COVID-19; tenofovir disoproxil fumarate; emtricitabine; baricitinib.

Received 24 May 2022; editorial decision 27 July 2022; published online 30 July 2022

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https://doi.org/10.1093/cid/ciac628

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There is controversy about the possible efficacy of tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) for the prevention and treatment of coronavirus disease 2019 (COVID-19). Several studies reported potential in silico [1] and in vitro [2] activity of TDF against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), while other in vitro studies found no antiviral activity [3, 4]. One animal model reported that ferrets treated with TDF/FTC had lower viral titers in nasal washes at day 8 postinfection than the control group [5]. Epidemiological studies have reported that people living with human immunodeficiency virus (HIV) receiving treatment with TDF/FTC compared to those receiving other antiretrovirals have a lower risk of SARS-CoV-2 seropositivity [6] and a lower risk of COVID-19–related hospitalizations [7]. In one cohort of people treated for chronic hepatitis B, better COVID-19 outcomes were reported among TDF/FTC users than for entecavir users [8]. One pilot randomized clinical trial of patients with nonsevere COVID-19 found that TDF/FTC appeared to accelerate clearance of nasopharyngeal SARS-CoV-2 [9]. One pragmatic trial in hospitalized patients found no effect on mortality or other clinical outcomes in the participants who received treatment with TDF/FTC [10]. However, in this pragmatic trial, participants treated with a combination of rosuvastatin plus colchicine plus TDF/FTC had a decrease in 28-day mortality risk and the need for invasive mechanical ventilation. Apart from a possible antiviral effect, several studies have reported that TDF/FTC decreases inflammatory cytokine production (interleukin 8 [IL-8], interleukin-10 [IL-10], monocyte chemoattractant protein 1 [MCP-1]) in peripheral blood mononuclear cells and might shift cytokine balance toward interleukin 12 [11, 12]. This shift would promote a Th1 response leading to production of interferon-gamma (IFN-γ) by T cells and natural killer cells. This effect may attenuate severe COVID-19 disease characterized by increases of IL-8, IL-10, and MCP-1 [13].

Baricitinib is an oral selective inhibitor of Janus kinase 1 and 2 that has already shown to improve clinical outcomes in randomized clinical trials of hospitalized patients with severe COVID-19 [14–16]. It might potentially exert combined antiviral and anti-inflammatory effects [17]. The antiviral effect is thought to be mediated by interfering with AP2-associated protein kinase 1, which would prevent SARS-CoV-2 cellular entry. Its anti-inflammatory effect is due to the inhibition of intracellular signaling pathways of cytokines such as interleukin 2, interleukin 6 (IL-6), IL-10, IFN-γ, and granulocyte–macrophage colony-stimulating factor [18].

Because TDF/FTC might have an antiviral and an immunomodulatory effect that could be synergistic with baricitinib, we have conducted a pragmatic randomized clinical trial to evaluate whether patients with high risk for severe COVID-19 would benefit from the possible antiviral/immunomodulatory activity of TDF/FTC followed by baricitinib in case of respiratory insufficiency accompanied by increased biomarkers of systemic inflammation.

METHODS

Study Design and Participants

The PANCOVID study is an open-label, stratified, double-randomized, phase 3 pragmatic clinical trial conducted in 25 sites in Spain led by La Paz University Hospital. The scheme of the study design is provided in Supplementary Figure 1. We recruited patients with symptomatic SARS-CoV-2 detected by polymerase chain reaction (PCR) or antigenic test in nasopharyngeal swabs, aged ≥60 years, or younger if they had at least 2 comorbidities (hypertension, obesity, diabetes, cirrhosis, chronic neurologic disease, active cancer, heart failure, coronary heart disease, or chronic obstructive pulmonary disease). Main exclusion criteria were creatinine clearance <60 mL/minute, receiving steroids at immunosuppressive doses (≥15 mg/day in the 7 days prior to the onset of symptoms), HIV infection, and severe respiratory failure (requiring a reservoir bag, mechanical ventilation, or acute respiratory distress) at the time of inclusion. The inclusion criteria for the second randomization were to have a room air oxygen blood saturation <95% and at least 1 increased inflammatory biomarker (IL-6, C-reactive protein, D-dimer, and/or ferritin). Full inclusion and exclusion criteria for both randomizations are detailed in the study protocol (see Supplementary Material). All participants provided written informed consent before inclusion.

The trial was undertaken in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. The trial protocol was approved by the Spanish Agency of Medicines and Health Products and by the La Paz University Hospital Research Ethics Board. This clinical trial was registered with EudraCT (2020-001156-18).

Randomization and Masking

In the first randomization, eligible participants were randomly assigned in a 1:1 ratio to receive or not receive TDF/FTC. At any moment during the trial participants could undergo a second randomization (1:1 ratio) to receive baricitinib plus dexamethasone or dexamethasone alone. The randomization list was centrally generated using SAS software, version 9.4; randomization was stratified by age group, symptom duration (<5 or ≥5 days), and healthcare setting (hospitalized, long-term care facility, ambulatory) to achieve balanced groups. The randomization list was imported into the secure Research Electronic Data Capture platform (REDCap, version 8.7.4) used for the study electronic case report form.

Procedures

The trial and evaluations followed a pragmatic approach as close as possible to clinical practice in an emergency such as the present pandemic. The dosing for TDF/FTC (200/245 mg) after first randomization was 2 oral tablets on the first day and 1 tablet daily for a total of 14 days. The dosing for

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baricitinib, based on a prior clinical trial [15], after second randomization was 4 mg once a day for 10–14 days, at the discretion of the investigator. For patients aged >75 years, the dose of baricitinib was reduced to 2 mg once a day. The dosing for dexamethasone was 6 mg daily (oral or intravenously) for 7–10 days, at the discretion of the investigator based on World Health Organization (WHO) guidelines [19].

At the discretion of the investigator, patients could also receive remdesivir. Patients were followed up on days 7, 14, and 28 after randomization, recording at least vital signs, blood test, and documentation of respiratory status. Patients entering the second randomization had an additional visit on day 7 after this randomization. If patients remained hospitalized on day 28, they were followed until discharge or death. Full procedure details are provided in the study protocol (Supplementary Material).

Outcomes

The primary outcome was 28-day mortality. Main secondary outcome was the combined variable disease progression (defined by increased oxygen requirements or intensified medical therapy including increased steroid dose and/or need for tocilizumab) or critical care unit admission or mortality. Other secondary outcomes were time in days to death, hospital admission (in ambulatory patients), critical care unit admission, need for second randomization, first negative PCR result for SARS-CoV-2, hospital discharge, and disease progression. Primary safety outcomes were percentage of patients with adverse events leading to discontinuation of treatment and percentage of patients with adverse events.

Statistical Analysis

Based on mortality data during the first COVID-19 wave in Spain, sample size calculations assumed a 20% mortality in this mixed population [20]. We also assumed an α error of .025, β error of .2, and a 0.7 risk reduction in mortality. resulting in a predefined sample of 1482 patients for each group (TDF/FTC vs no TDF/FTC). The trial was stopped before reaching the planned sample size due to the decrease in the number of COVID-19 cases during the recruitment period and the much lower global mortality observed.

The main results were summarized as absolute and relative frequencies in the case of qualitative variables, and median and interquartile range (IQR) in the case of quantitative variables. The main outcome (28-day mortality), main combined secondary endpoint (disease progression/critical care unit admission/28-day mortality), and other secondary outcomes were compared between treatment groups (TDF/FTC vs no TDF/FTC, baricitinib plus dexamethasone vs dexamethasone alone) using Fisher exact test. In addition, their respective relative risks and 95% confidence intervals (CIs) were calculated.

The comparison of continuous variables between the treatment groups (eg, age, days since first randomization until death, laboratory parameters) was performed using the Mann-Whitney *U* test, due to the nonnormality of most of the continuous variables. For multiple comparisons of treatment groups, the *P* value was adjusted by the Bonferroni method. Subsequently, Tukey and Bonferroni post hoc tests were performed. We performed a logistic regression analysis to evaluate a interaction between TDF/FTC and baricitinib including age, sex, number of comorbidities, simultaneous or deferred randomization, and randomization group. Statistical analysis was performed with R software (version 4.1.1., Vienna, Austria). For the primary outcome of 28-day mortality, the results from the PANCOVID trial were subsequently included in a meta-analysis of results from all previous randomized controlled trials of baricitinib for patients hospitalized with COVID-19. Details of the systematic search and meta-analysis methods are provided in the Supplementary Material.

RESULTS

From 10 October 2020 to 23 September 2021, a total of 355 patients from 25 hospitals in Spain were enrolled in the trial and underwent the first randomization. Of these 355 patients 344 were hospitalized, 4 were residents of long-term care facilities and 7 were ambulatory. In this first randomization, 177 and 178 patients were respectively assigned to receive or not TDF/FTC. Of these 355 patients, 287 underwent the second randomization to receive baricitinib plus dexamethasone or dexamethasone alone, 264 immediately after the first randomization and 23 subsequently. A total of 45 patients also received remdesivir. A total of 338 patients (TDF/FTC, n = 167; no TDF/FTC, n = 171), completed the 28-day follow-up, whereas 11 died and 6 patients discontinued the study (Figure 1).

Baseline demographic and disease characteristics were generally balanced between the first randomization treatment groups (Table 1). Most patients were men (64%), and the median age was 67 years (IQR, 62–73 years). On average, patients were randomized 7 days after symptom onset. Twenty-three percent of patients did not have any comorbidities, 30% had 1 comorbidity, and 47% had at least 2 comorbidities. The most frequent comorbidity was hypertension (61% patients), followed by diabetes (27%) and obesity (16%). Thirty-seven percent patients did not need ventilation support, while 60% needed nasal cannula, 1% conventional mask, and 1% high-flow device; only 1 patient needed a rebreathing mask. Inflammatory biomarkers were also similar between groups. Of the 291 participants for whom vaccination status was known, 267 (91%) had received at least 1 dose of a SARS-CoV-2 vaccine. Baseline demographic and disease characteristics were in general also well balanced between the second randomization treatment groups except for the number

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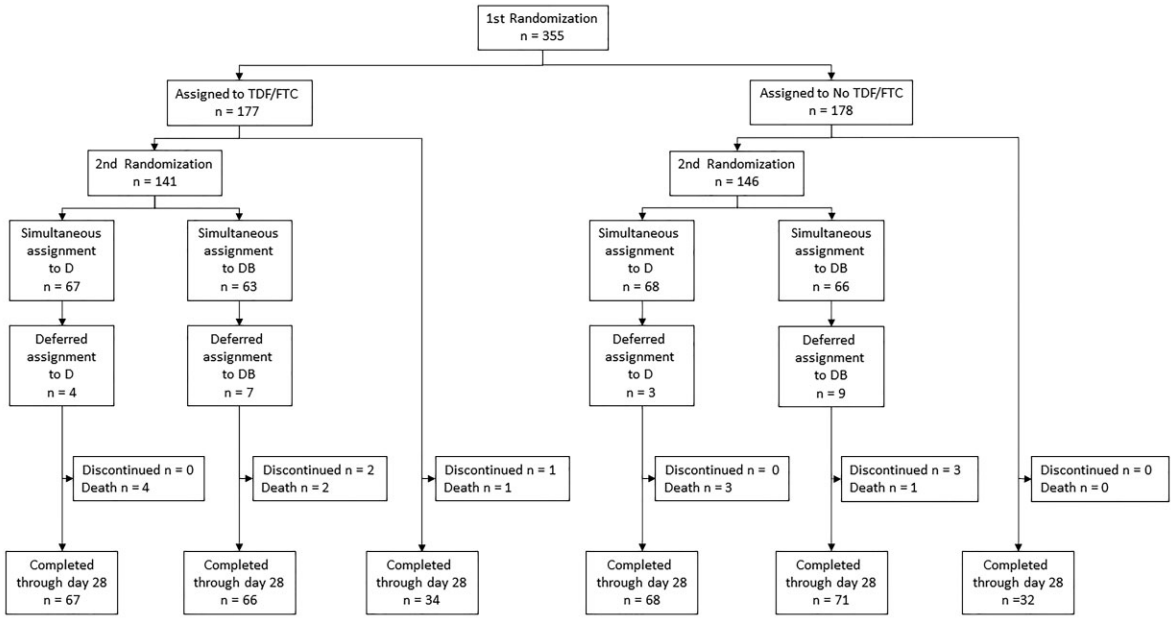

Figure 1. Trial profile. Abbreviations: D, dexamethasone; DB, dexamethasone and baricitinib; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

of comorbidities that were numerically higher in the dexamethasone group without reaching statistical significance (Table 2). Patients undergoing the second randomization had similar characteristics to the whole group, apart from oxygen support (any kind) and inflammatory biomarker levels. Oxygen support was needed by 62% of patients included in the first randomization and by 74% of those patients included in the second one. Also, median levels of inflammatory biomarkers were slightly higher in patients who underwent the second randomization.

Regarding primary and secondary efficacy outcomes of the first randomization (ie, TDF/FTC compared to no TDF/FTC), overall 28-day mortality was 3.1%, with no statistical difference between groups (Table 3). The primary outcome occurred in 7 patients in the TDF/FTC group (4.0%) and 4 in the no TDF/FTC group (2.2%). The relative risk (RR) for 28-day mortality was 1.76 (95% CI, .52–5.91; $P = .379$) (Table 3). The main combined secondary outcome, including disease progression or critical care unit admission or 28-day mortality, was similar between groups (TDF/FTC, 22.0%; no TDF/FTC, 23.6%). The RR for the composite outcome was 0.95 (95% CI, 0.66–1.40; $P = .774$) (Table 3). The other secondary efficacy outcomes did not reach statistical difference between groups (Table 3).

Regarding primary and secondary efficacy outcomes of the second randomization (ie, baricitinib plus dexamethasone compared to dexamethasone alone), overall 28-day mortality in 287 patients entering in the second randomization was 3.5% (Table 4). The primary outcome occurred in 3 patients in the baricitinib plus dexamethasone group (2.1%) and 7 in the dexamethasone alone group (4.9%). Despite an RR of 0.42 for mortality in the baricitinib plus dexamethasone group, statistical significance was not achieved (95% CI, .11–1.59; $P = .201$) (Table 4). The occurrence of the main combined secondary outcome in the baricitinib plus dexamethasone and the dexamethasone alone groups was 24.8% and 27.5%, respectively. The RR for the composite outcome was 0.90 (95% CI, .61–1.33; $P = .687$) (Table 4). Results of the rest of the secondary efficacy outcomes did not achieve statistically significant difference between groups (Table 4). Comparison of main outcomes of this randomization stratified by the group of the first randomization are presented in Supplementary Table 1. No statistically significant differences were found among the 4 groups. No interaction between TDF/FTC and baricitinib were identified according to results from the logistic regression model.

Regarding safety, 208 patients presented a total of 233 adverse events (Supplementary Tables 2 and 3). Adverse events were more frequent in patients who underwent the second randomization. Serious adverse events were reported in 13 (Supplementary Table 2). The most common adverse event was hyperglycemia, followed by increased alanine aminotransferase/aspartate aminotransferase, diarrhea, and constipation (Supplementary Table 3). Eight patients developed an adverse event leading to discontinuation of treatment (Supplementary Table 2).

Our systematic search identified 4 previous trials and 1 meta-analysis [21] of baricitinib, involving a total of 10 815

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Table 1. Patient Characteristics and Baseline Values at First Randomization: Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC) Versus No TDF/FTC

Characteristic	All Patients (N = 355)	TDF/FTC (n = 177)	No TDF/FTC (n = 178)
Sex, female	126 (35.5)	64 (36.2)	62 (34.8)
Age, y			
Median (IQR)	67.0 (62.0–73.0)	68.0 (62.0–74.0)	67.0 (62.2–73.0)
≤60	61 (17.2)	28 (15.8)	33 (18.5)
>60	294 (82.8)	149 (84.2)	145 (81.5)
Time from symptom onset to first randomization, d			
Median (IQR)	7.0 (5.0–10.0)	8.0 (5.0–10.0)	7.0 (5.0–10.0)
≤5	106 (29.9)	52 (29.4)	54 (30.3)
>5	249 (70.1)	125 (70.6)	124 (69.7)
Comorbidities			
None	82 (23.1)	37 (20.9)	45 (25.3)
1	105 (29.6)	55 (31.1)	50 (28.1)
≥2	168 (47.3)	85 (48.0)	83 (46.6)
Hypertension	217 (61.1)	112 (63.3)	105 (59.0)
Diabetes	97 (27.3)	52 (29.4)	45 (25.3)
Obesity	57 (16.1)	27 (15.3)	30 (16.9)
Oxygen saturation, %, median (IQR)	95.0 (94.0–96.0)	95.0 (94.0–96.5)	95.0 (94.0–96.0)
Oxygen support			
None	133 (37.5)	65 (36.7)	68 (38.2)
Nasal cannula	214 (60.3)	108 (61.0)	106 (59.6)
Conventional mask	3 (0.8)	2 (1.1)	1 (0.6)
High-flow device	4 (1.1)	1 (0.6)	3 (1.7)
Rebreathing mask	1 (0.3)	1 (0.6)	0 (0.0)
Inflammatory biomarkers, median (IQR)			
CRP, mg/L	61.7 (30.3–107.5)	63.80 (30.7–117.0)	58.40 (30.1–96.9)
LDH, U/L	285.0 (232.5–371.5)	299.0 (235.7–374.7)	280.00 (232.0–356.0)
D-dimer, ng/mL	406.00 (12.3–650.0)	417.00 (9.9–700.0)	380.00 (12.4–590.7)
IL-6, pg/mL	17.40 (6.8–37.2)	20.00 (7.1–36.1)	14.00 (6.8–38.1)
Remdesivir prior/after first randomization	45 (12.7)	23 (12.9)	22 (12.4)
Anti-inflammatory treatment (second randomization)	287 (80.8)	141 (79.7)	146 (82.0)
Simultaneous with first randomization			
Dexamethasone	135 (47.0)	67 (47.5)	68 (46.6)
Dexamethasone + baricitinib	129 (44.9)	63 (44.7)	66 (45.2)
Deferred after first randomization			
Dexamethasone	7 (2.4)	4 (2.8)	3 (2.1)
Dexamethasone + baricitinib	16 (5.6)	7 (5.0)	9 (6.2)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CRP, C-reactive protein; IL-6, interleukin 6; IQR, interquartile range; LDH, lactate dehydrogenase; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

randomized patients and 1331 deaths [14–16, 22] (Figure 2). After inclusion of the results from PANCOVID trial into this meta-analysis, the overall mortality risk ratio from all 5 trials—now involving 11 102 randomized patients and 1341 deaths—was 0.73 (95% CI, .57–.92; $P = .008$) (Figure 2).

DISCUSSION

In this pragmatic randomized clinical trial, we have not found evidence that treatment with TDF/FTC improves clinical outcomes in hospitalized patients with COVID-19 at high risk of disease progression. There were no statistical significant differences between participants treated and not treated with TDF/FTC for the primary endpoint of reduction of mortality at day 28, neither for the combined secondary endpoint of disease progression nor intensive care unit admission or 28-day mortality. For both outcomes, the lower limit of the 95% CI was above the 0.7 risk reduction established as the difference to detect in our sample size calculations.

In our trial, patients who needed oxygen therapy and had at least 1 increased inflammatory biomarker were additionally randomized to dexamethasone with or without baricitinib. For this second randomization, there were no statistically significant differences between the groups for the primary endpoint of reduction of mortality at day 28 or for the main combined secondary endpoint of disease progression or critical care unit admission or 28-day mortality.

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Table 2. Patient Characteristics and Baseline Values for Second Randomization: Baricitinib Plus Dexamethasone Versus Dexamethasone

Characteristic	All Patients (N = 287)	Baricitinib Plus Dexamethasone (n = 145)	Dexamethasone (n = 142)
Sex, female	99 (34.5)	51 (35.2)	48 (33.8)
Age, y			
Median (IQR)	67.0 (62.0–74.0)	68.0 (63.0–75.0)	67.0 (61.0–72.7)
≤60	61 (17.2)	23 (15.9)	30 (21.1)
>60	294 (82.8)	122 (84.1)	112 (78.9)
Time from symptom onset to second randomization, d			
Median (IQR)	7.0 (5.0–10.0)	8.0 (5.0–11.0)	7.0 (5.0–9.7)
≤5	83 (28.9)	37 (25.5)	46 (32.4)
>5	204 (71.1)	108 (74.5)	96 (67.6)
Time from first to second randomization (excluding simultaneous randomization), d, median (IQR)	1.0 (1.0–2.0)	1.00 (1.0–2.0)	2.0 (1.0–2.5)
Comorbidities			
None	76 (26.5)	43 (29.7)	33 (23.2)
1	83 (28.9)	44 (30.3)	39 (27.5)
≥2	128 (44.6)	58 (40.0)	70 (49.3)
Diabetes	85 (29.6)	37 (25.5)	48 (33.8)
Hypertension	165 (57.5)	78 (53.8)	87 (61.3)
Obesity	54 (18.8)	27 (18.6)	27 (19.0)
Oxygen saturation, %, median (IQR)	95.0 (94.0–96.0)	95.00 (94.0–96.0)	95.00 (93.0–96.0)
Oxygen support			
None	74 (25.8)	42 (29.0)	32 (22.5)
Nasal cannula	205 (71.4)	99 (68.3)	106 (74.6)
Conventional mask	3 (1.0)	3 (2.1)	0 (0.0)
High-flow device	4 (1.4)	1 (0.7)	3 (2.1)
Rebreathing mask	1 (0.3)	0 (0.0)	1 (0.7)
Inflammatory biomarkers, median (IQR)			
CRP, mg/L	66.7 (33.6–113.7)	68.1 (33.8–113.6)	65.4 (33.6–113.6)
LDH, U/L	304.0 (242.0–378.0)	303.5 (238.5–371.7)	305.0 (247.0–379.0)
D-dimer, ng/mL	417.5 (15.4–655.5)	430.0 (35.0–665.0)	410.0 (9.4–640.0)
IL-6, pg/mL	17.7 (6.5–37.3)	19.2 (7.8–43.4)	12.0 (6.0–29.9)
Remdesivir prior to/at first randomization	44 (15.3)	22 (15.2)	22 (15.5)
TDF/FTC prior to/at second randomization	141 (49.1)	71 (48.9)	70 (49.3)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CRP, C-reactive protein; IL-6, interleukin 6; IQR, interquartile range; LDH, lactate dehydrogenase; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Our study is limited mainly because our estimates of the efficacy of treatment with TDF/FTC and baricitinib are imprecise with wide CIs. This limitation derives from our limited sample size and the unexpected low mortality observed in our trial. The overall mortality in our trial was 3.1%; even though our participants had a median age of 67 years, 76.9% had at least 1 comorbidity predisposing to severe COVID-19 and almost all of them were hospitalized when randomized. Taking this low mortality into account, we would have needed >5000 patients per group to detect a 30% reduction in mortality between groups (3.1 vs 2.17). Our results are also limited by the lack of virological data. Although the protocol planned to study virological endpoints, due to the situation in most hospitals, required samples were not collected. Another limitation is our open-label design, which is common in pragmatic clinical trials [23] with hard endpoints such as mortality.

In 3 other trials of baricitinib for hospitalized patients with COVID-19 not requiring mechanical ventilation, overall reported mortality at day 28 was higher than in PANCOVID. In the Adaptive COVID-19 Treatment Trial 2 (ACTT-2) trial [15], mean patient age was 55.4 years and mortality was 5.9%. In the Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Study of Baricitinib in Patients with COVID-19 Infection (COV-BARRIER) trial [14], patients' mean age was 57.6 years and mortality was 10.6%. In the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial [16], mean age was 58.1 years and mortality at day 28 was 13%. One possible explanation for the lower mortality (3.1%) in PANCOVID is that 25.8% of our participants did not need oxygen therapy at baseline, while this proportion was 13.7% in ACTT-2, 12.2% in COV-BARRIER, and very small (exact data not provided) in the RECOVERY trial. Although patients in PANCOVID were almost 1 decade older than those enrolled in ACTT-2, COV-BARRIER, and RECOVERY, it is possible that they could have had less severe disease at baseline. It is also possible that, being a more recent trial, the higher proportion of

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Table 3. Disease Outcomes for First Randomization: Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC) Versus No TDF/FTC

Variable	TDF/FTC (n = 177)	No TDF/FTC (n = 178)	RR (95% CI)	*P* Value
Primary outcome				
28-d mortality	7 (4.0)	4 (2.2)	1.76 (.52–5.91)	.379
Secondary outcomes				
Disease progression/critical care unit admission/28-d mortality (combined)	39 (22.0)	42 (23.6)	0.95 (.66–1.40)	.774
Disease progression	39 (22.0)	42 (23.6)	0.94 (.66–1.35)	.774
Increase of oxygen support	36 (35.6)	40 (37.7)	0.95 (.71–1.28)	.867
Increase of steroid dose	19 (19.0)	19 (17.9)	0.94 (.53–1.68)	.859
Need for new medication	21 (21.0)	27 (25.5)	0.82 (.50–1.36)	.511
Tocilizumab	7 (4.0)	12 (6.7)	…	
Other medication	14 (7.9)	15 (8.4)	…	
Mechanical ventilation				
Noninvasive (BiPAP, CPAP, HFNC)	8 (4.5)	5 (2.8)	0.90 (.51–1.59)	.589
Invasive	8 (4.5)	13 (7.3)		
Days since first randomization until death, median (IQR)	17.0 (10.5–26.5)	25.5 (24.7–34.7)	8.5 (–10.0 to 31.5)	.218
Days since first randomization until discharge, median (IQR)	6.0 (4.0–12.0)	7.0 (5.0–14.0)	1.0 (–2.0 to 1.0)	.369
Discharge ≤28 d	148 (89.7)	159 (91.9)	1.27 (.65–2.50)	.573
Discharge >28 d	17 (10.3)	14 (8.1)		

Data are presented as No. (%) unless otherwise indicated. Mann-Whitney *U* test for continuous variables and χ^2 test for qualitative variables.

Abbreviations: BiPAP, bilevel positive airway pressure; CI, confidence interval; CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannula; IQR, interquartile range; RR, relative risk; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

patients in PANCOVID who had received at least 1 dose of a SARS-CoV-2 vaccine might have contributed to a decreased mortality. Vaccination status was only reported in the RECOVERY trial where 42% patients had received at least 1 dose of a SARS-CoV-2 vaccine compared to 91.2% in PANCOVID.

Despite the imprecision of our estimate for the efficacy of TDF/FTC, our interpretation of the results is that it is unlikely that TDF/FTC can have a relevant beneficial effect when used in hospitalized patients with COVID-19. This interpretation agrees with another recent pragmatic trial that did not find a positive effect of TDF/FTC in hospitalized patients with

Table 4. Disease Outcomes for Second Randomization: Baricitinib Plus Dexamethasone Versus Dexamethasone

Variable	Baricitinib Plus Dexamethasone (n = 145)	Dexamethasone (n = 142)	RR (95% CI)	*P* Value
Primary outcome				
28-d mortality	3 (2.1)	7 (4.9)	0.42 (.11–1.59)	.201
Secondary outcomes				
Disease progression/critical care unit admission/28-d mortality (combined)	36 (24.8)	39 (27.5)	0.90 (.61–1.33)	.687
Disease progression	36 (24.8)	39 (27.5)	0.90 (.61–1.33)	.687
Increase of oxygen support	34 (37.0)	36 (39.6)	0.93 (.65–1.35)	.762
Increase of steroid dose	20 (21.7)	15 (16.7)	1.30 (.71–2.38)	.453
Need for new medication	22 (23.9)	21 (23.3)	1.02 (.61–1.73)	1.000
Tocilizumab	5 (3.4)	13 (9.2)	…	
Other medication	17 (11.7)	8 (5.6)	…	
Mechanical ventilation				
Noninvasive (BiPAP, CPAP, HFNC)	3 (2.1)	8 (5.6)	0.64 (.33–1.27)	.378
Invasive	9 (6.2)	11 (7.7)		
Days since first randomization until death, median (IQR)	28.0 (26.5–44.5)	24.0 (14.5–25.5)	–4.0 (–49.0 to 1)[a]	.110
Time since first randomization until discharge, d, median (IQR)	7.0 (5.0–13.5)	7.00 (5.0–12.0)	0.0 (–3.0 to .0)[a]	.596
Discharge ≤28 d	131 (94.2)	121 (89.0)	0.52 (.22–1.19)	.131
Discharge >28 d	8 (5.8)	15 (11.0)		

Data are presented as No. (%) unless otherwise indicated. Mann-Whitney *U* test for continuous variables and χ^2 test for qualitative variables.

Abbreviations: BiPAP, bilevel positive airway pressure; CI, confidence interval; CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannula; IQR, interquartile range; RR, relative risk.

[a]Median difference.

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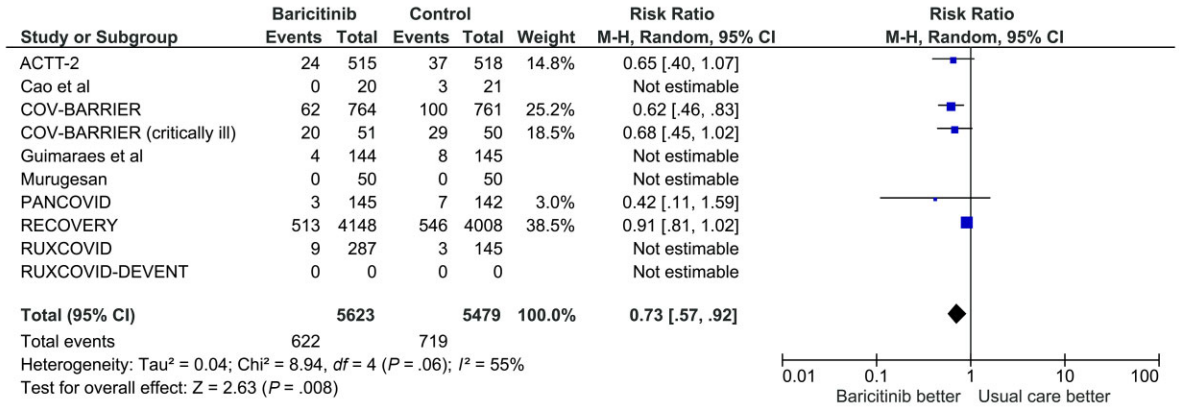

Figure 2. Baricitinib vs usual care in patients hospitalized with coronavirus disease 2019. Meta-analysis of mortality in PANCOVID and other trials, including weight and risk ratio (95% confidence interval [CI]) of each trial, heterogeneity analysis, and pooled risk ratio with a 95% CI using the Mantel-Haenszel method under a random-effects model. Abbreviations: CI, confidence interval; *df*, degrees of freedom; M-H, Mantel-Haenszel.

COVID-19 [10]. Our study does not rule out a possible beneficial effect of TDF/FTC when used earlier during infection. Of note, participants in our trial started treatment with TDF/FTC a median time of 7 days after symptom onset. Other antivirals such as molnupiravir have demonstrated to improve outcomes only in ambulatory patients when started within 5 days after the onset of signs or symptoms of COVID-19 [24] but not in hospitalized patients with a longer duration of symptoms [25]. Our initial goal when we designed the trial was to include a substantial number of ambulatory participants. Unfortunately, the situation in primary care settings during the beginning of the trial did not permit us to include a significant number of them.

Our estimates about the efficacy of baricitinib are also imprecise. For this reason we included our results in a meta-analysis of all published trials of baricitinib for treatment of COVID-19 [14–16, 22]. The results of this updated meta-analysis confirm the positive effect of baricitinib on mortality as shown by a 27% decrease in mortality. Currently the WHO guidelines [19] provide a strong recommendation for the use of baricitinib as an alternative to IL-6 receptor blockers, in combination with corticosteroids, in patients with severe or critical COVID-19.

In summary, results of this randomized clinical trial exploring the efficacy of TDF/FTC for the treatment of hospitalized patients with COVID-19 at high risk of disease progression do not suggest a beneficial effect of TDF/FTC, although our estimate of its effect is imprecise. The results of our updated meta-analysis of 5 clinical trials including PANCOVID support a substantial beneficial effect of baricitinib for the treatment of severe COVD-19.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. Trial conceptualization and design were done by A. J. C., A. M. B., and J. R. A. Analysis and interpretation of the data were done by R. M., F. C.-P., M. V., C. G., M. J.-G., A. J. C., A. M. B., and J. R. A. Critical revision of the article for important intellectual content was provided by R. M., F. C.-P., M. V., C. G., J. Q.-P., M. J.-G., P. G.-R., P. M., M. I., A. J. G., M. C., A. G., A. D.-B., M. T., P. R., C. M., C. D., S. I., E. M., V. E., J. M., M. N., M. A. R., M. R.-M., M. d. M., S. C., L. S., M. d. A., S. M., M. S., A. J. C., A. M. B., and J. R. A. Provision of study materials for patients was done by R. M., F. C.-P., M. V., C. G., P. G.-R., P. M., M. I., A. J. G., M. C., A. G., A. D.-B., P. R., C. M., C. D., S. I., E. M., V. E., J. M., M. N., M. A. R., M. R.-M., S. C., L. S., S. M., M. S., and J. R. A. Statistical expertise was provided by M. J.-G., A. J. C., A. M. B., and J. R. A. Obtaining of funding was managed by A. J. C., A. M. B., and J. R. A. Administrative, technical, or logistical support was provided by J. Q.-P. and M. d. M. Collection and assembling of data was carried out by J. Q.-P., M. J.-G., M. d. M., A. J. C., A. M. B., and J. R. A. All authors reviewed and edited the manuscript, and approved the manuscript for submission. All authors had full access to the full data in the study and accept responsibility to submit for publication.

Acknowledgments. The authors thank the members of PANCOVID team for their many contributions in conducting the trial; the members of scientific committee (Infectious Diseases Unit, Clinical Pharmacology Department, Emergency Department and Geriatric Department of La Paz University Hospital, Primary Care Direction of Comunidad de Madrid, and Fundación SEIMC-GESIDA); the members of the monitoring team (Fundación SEIMC-GESIDA); the members of management and coordination center (Clinical Trial Unit of La Paz University Hospital); the members of data management center (Instituto de Investigación Biosanitaria del Hospital 12 de Octubre); physicians and healthcare workers of participating institutions; and the patients for their altruism in participating in this trial. The authors also thank Esther Prieto for editorial assistance (employed by Hospital Universitario La Paz; funded by the Instituto de Salud Carlos III [grant number COV20/00023]).

Data sharing. The following supporting documents will be made available with publication: informed consent form, statistical analysis plan, and statistical analysis report. The following data will be made available with publication: complete anonymized patient data set (available from M. J.-G., e-mail: maria.jimenez.gonzalez@salud.madrid.org). Individual participant data will be made available when the trial is complete, on request to the corresponding author. After approval of the proposal, data will be shared through a secure online procedure.

Disclaimer. The funder had no influence on the design or conduct of the trial and were not involved in data collection or analysis, manuscript writing, or the decision to submit it for publication.

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Financial support. This clinical trial was funded by the Instituto de Salud Carlos III (ISCIII), Ministry of Innovation and Science of Spain, in a competitive and public grant (Royal Decree-Law 8/2020, of 17 March, on extraordinary urgent measures to face the economic and social impact of COVID-19). Project code: COV20/00023 (co-funded by European Regional Development Fund/European Social Fund "A way to make Europe"/"Investing in your future"). Baricitinib was provided by Eli Lilly, and tenofovir disoproxil fumarate/emtricitabine was partially provided by Teva. The clinical trial was designed and the data analyzed by the senior authors and the biostatistician.

Potential conflicts of interest. P. R. has received grant support and honoraria from Gilead and MSD; consulting fees from AbbVie SL; payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing, or educational events from ViiV and Gilead Sciences; and support for attending meetings and/or travel from AbbVie and GSK (ViiV). J. V. has received scholarships and honorarium as speaker for Gilead Sciences. M. S. has received honoraria from Gilead; has developed educational material for MSD and ViiV Healthcare; and has served on advisory boards for MSD and Gilead. A. M. B. reports grants or contracts from GSK, Moderna, and Janssen (paid to institution); advisory fees from Janssen and Pfizer (paid to author); participation on a data and safety monitoring board (DSMB) for Pfizer, Janssen, and Medical Developments International (paid to author); payment or honoraria for lectures, presentations, manuscript writing, or educational events from Gilead and Pfizer (paid to author); and speaker's fees from Janssen (paid to author). J. R. A. reports payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing, or educational events from Merck (paid to author); support for attending meetings and/or travel from MSD (paid to author); and consulting fees, advisory fees, and speaker's fees from Gilead, Merck, Pfizer, Sobi, GSK, MSD, Serono, Lilly, and Roche (paid to author); he is also a member of the Infectious Diseases and Clinical Microbiology Society COVID-19 treatment guidelines. A. G. L. reports payment or honoraria for presentation from Gilead Sciences, and support for attending meetings and/or travel from Angelini Pharma España. A. J. C. reports grants or contracts from ISCIII, Ministry of Innovation and Science of Spain (PI21/01507, PI18/00136, CM19/00243, ICI21/00065), and Vaccelerate (Clinical trial name: EU-Covat-1 Aged); payment or honoraria for a course on clinical investigation (paid to institution) from AbbVie, and participation on a DSMB or advisory board for AMR Insights (paid to institution). C. G. reports consulting fees, participation on a DSMB or advisory board, and payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing, or educational events from Amgen, Daiichi Sankyo, Ferrer, and Sanofi; and support for attending meetings and/or travel from Sanofi and Ferrer. L. S. reports grants or contracts from Novartis and Boehringer, and support for attending meetings and/or travel from Novartis. M. R.-M. reports support for attending meetings and/or travel from Roche Farma SA. M. N. M. reports support for attending meetings and/or travel and payment/honoraria for presentations and educational events from Gilead. M. V. A. reports grants or contracts from Gilead and ViiV (paid to institution); payment or honoraria for lectures and educational events for Gilead and Janssen (paid to author and institution); payment or honoraria for educational events from ViiV and MSD (paid to institution); and support for attending meetings and/or travel from Angelini, Gilead, and Janssen (paid to author). P. G.-R. P. reports support for attending meetings and/or travel from Gilead and Angelini. P. M. reports payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing, or educational events from Sanofi (paid to author). R. M. reports payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing, or educational events from Gilead, ViiV, Merck Sharp & Dohme, and Theratechnologies (paid to author); payment for expert testimony from Gilead and ViiV (paid to author); support for attending meetings and/or travel from Gilead and Janssen (paid to author); and participation on a DSMB or advisory board for ViiV (paid to author). S. M. reports payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing, or educational events from Pfizer, Gilead, Roche, Sobi, and MSD (paid to author), and participation on DSMBs or advisory boards for Pfizer, Gilead, and MSD (paid to author). V. E. reports consulting fees from Gilead, Janssen, and MSD (paid to author); payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing, or educational events from Gilead and Janssen (paid to author); support for attending meetings and/or travel from Gilead (paid to author); and participation on DSMBs or advisory boards for Gilead, Janssen, and Synairgen (paid to author). None of the listed potential conflicts are related to this work. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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