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Early View

Research letter

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SECOND REVISION

ADD-ON INHALED BUDESONIDE IN THE TREATMENT OF HOSPITALIZED PATIENTS WITH COVID-19: A RANDOMIZED CLINICAL TRIAL

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SARS-CoV-2 vaccines have been extremely effective to reduce the incidence of severe COVID19 [1-3], but effective and safe treatments of the acute infection are still limited [4, 5]. An uncontrolled pulmonary inflammatory response to SARS-CoV-2 is considered a key pathogenic mechanism of COVID19 progression [6], so systemic dexamethasone is recommended in severe cases [5, 7]. On the other hand, in very mild patients at home inhaled corticosteroids (ICS) may prevent disease progression [8-11]. Whether ICS prevent disease progression too in patients hospitalized because of COVID19 has not been explored before. Accordingly, we designed an investigator-initiated, open-label, randomized clinical trial (RCT) to explore the efficacy of adding inhaled budesonide to usual care to prevent disease progression in patients hospitalized because of COVID19 pneumonia. We also monitored carefully the safety of this intervention since there are concerns about the use of systemic corticosteroids in other viral (influenza) lung infections [12].

METHODS

The "Inhaled Corticosteroid Treatment of COVID19 Patients With Pneumonia" (TACTIC) was a multicentre, international (Spain and Argentina), randomized (1:1), open label RCT (NCT04355637) whose primary objective was to investigate if the addition of inhaled budesonide (400μg/12 h via Pulmicort Turbuhaler®) to usual care (as dynamically established by the institutional protocol of each participating centre during the course of the pandemic) prevents disease progression, defined by a composite outcome that included treatment with non-invasive ventilation of high flow oxygen devices (WHO stage 5), invasive ventilation (WHO stage 6) and/or death from any cause (WHO stage 7) [13] during the first 15 days after randomization.

We studied males and females between 18-80 years of age hospitalized because of PCR confirmed SARS-CoV-2 infection, with radiological evidence (plain chest x-ray) of pneumonia, without any contraindication to the study drug, who provided informed consent. Exclusion criteria included previous treatment with inhaled or systemic steroids (e.g., dexamethasone) and/or other immunomodulator drugs (e.g., anti-interleukins), high flow-oxygen or mechanical ventilation, and pregnancy. This RCT was approved by the Institutional Review Boards of participating institutions and was supported by AstraZeneca, who generously provided the study medication for free and economic support for logistics costs but did not participate in the design of the study, data analysis and/or writing of the manuscript. The Clinical Trial Unit of Fundació Clinic per la Recerca Biomedica-Hospital Clinic (Barcelona, Spain) monitored the trial in coordination with Klixar (in participating centres in Argentina), centralized all investigational information, and assured the quality control of results.

Based on available knowledge at the time of trial design (March 2020), we hypothesized that this would occur in 15% of patients randomized to the usual care arm and 5% of those included in the intervention arm. Then, for a two-sided type I error of 5% and power of 80% and 5% estimated losses during follow-up, with three prespecified interim analyses designed using the Rho family spending functions with rho = 7 and a recalculation of sample size at 75% of expected events, we estimated that 300 patients (150 per arm) would be needed to be randomized, (East v6.5 Cytel Inc., Cambridge, MA). Randomization (1:1) was made by a permuted-block method with a block size of multiple of 2 elements and was stratified by centre with an interactive web service. The primary endpoint of the study was estimated by comparing the proportion

of patients with disease progression (defined as above) in both arms using a binomial regression model, adjusted for centre (grouped by country) as covariate [14, 15]. Time-to-event analyses was described by means of the Kaplan-Meier method and inferential analyses was made by means log-rank test. All analyses were carried out by the Medical Statistics Core Facility of IDIBAPS-Hospital Clinic Barcelona (Spain) and performed using SAS v9.4 (SAS Institute Inc Cary, NC, USA)

RESULTS

From April 21, 2020 until March 16 2021, we randomized 120 patients (Full Analysis Set (FAS)). Because the progressive and generalized use of dexamethasone to treat hospitalized patients with COVID-19 [5] limited greatly our capacity to continue recruiting patients who had not received it before randomization, the steering committee of the study decided to stop the study prematurely in April 2021.

As shown in Table 1, both groups were comparable in terms of demographics and main clinical and radiological characteristics at randomization, albeit the proportion of patients without supplemental oxygen at entry was nominally higher in the usual care group (n=49 (79.0%) *vs.* n=40 (69.0%)). Disease progression occurred in 4 patients (6.62%; 95% CI 0.45% to 12.79%) in the usual care group and 2 patients (3.74%; 95%CI -1.23% to 8.72%] in the usual care + budesonide one, difference being non-significant (-2.88% [95%CI -10.48% to 4.72%], p=0.458). Of note, 13 patients (21%) in the usual care arm were treated with dexamethasone after randomization at the discretion of the attending physician, whereas only 6 patients (10.7%) in the intervention group were. Importantly, adverse events were similar in both groups and

there were no treatment-related adverse events (Table 1). Two patients died during follow-up, both beyond day 30, 1 in the control group (due to liver cirrhosis) and 1 in the intervention group (due to COVID19) (log-rank p value = 0.9564).

DISCUSSION

This RCTs lacks statistical power because it had to be terminated prematurely. However, results suggest that the addition of inhaled budesonide to usual care in patients hospitalized because of COVID19 pneumonia is safe and showed an encouraging trend towards a reduction in disease progression. The fact that the proportion of patients not requiring oxygen supplementation at randomization was larger in the usual care group (hence, better pulmonary gas exchange at baseline), and that, despite this, a higher proportion of them received systemic dexamethasone at the discretion of the attending physician, provides additional indirect evidence of a beneficial clinical effect of inhaled budesonide to prevent disease progression. Finally, it is important to highlight that the use of an inhaled corticosteroid in these patients was safe. These results may open the door for larger RCT in the near future, now that a new pandemic wave seems to be emerging again in several countries around the world. Dexamethasone reduces mortality in patients requiring supplementary oxygen in hospital and is recommended by ERS guideline [5, 7], but is not recommended for patients not requiring supplementary oxygen, which accounted for 74% of our cohort. A safe treatment that could reduce disease progression in this patient group would still be desirable. In fact, three very recent reports have shown that the use of inhaled steroids can reduce disease progression in mostly asymptomatic COVID-19 patients treated at home [8-11]. The results of the current RCT extend these previous observations on the use of inhaled steroids in the community to patients hospitalized because of COVID-19

pneumonia. Future studies may also need to explore the efficacy and safety of higher doses of inhaled budesonide (800μg/12h), as previously investigated in milder patients at home [8].

In conclusion, the results of this RCT suggest that the addition of inhaled budesonide (400μg/12h) on top of usual care in patients hospitalized because of COVID-19 pneumonia is safe and may reduce the risk of disease progression.

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Table 1. Demographics and main clinical variables (n (%) or mean±SD) at randomization (FAS), concomitant medications received and adverse events (Safety population).

	Usual Care N=62	**Usual Care + Budesonide N=58**	**Total N=120**
Demographics (FAS)			
Age (years)	51.6 ± 13.8	50.6 ± 13.7	51.1 ± 13.7
Males	32 (51.6%)	24 (42.1%)	56 (47.1%)
Body mass index (Kg/m2)	30.1 ± 6.5	28.6 ± 6.0	29.4 ± 6.3
Smoker status			
Current	3 (4.8%)	1 (1.8%)	4 (3.4%)
Former	12 (19.4%)	10 (17.5%)	22 (18.5%)
Never	47 (75.8%)	46 (80.7%)	93 (78.2%)
Symptoms (FAS)			
Fever	53 (85.5%)	40 (70.2%)	93 (78.2%)
Cough	40 (64.5%)	40 (70.2%)	80 (67.2%)
Arthromyalgia	26 (41.9%)	26 (45.6%)	52 (43.7%)
Anosmia	19 (30.6%)	19 (33.3%)	38 (31.9%)
Ageusia	19 (30.6%)	17 (29.8%)	36 (30.3%)
Diarrhoea	16 (25.8%)	21 (36.8%)	37 (31.1%)
Chest x-ray findings (FAS)			
Bilateral pneumonia	48 (77.4%)	49 (86.0%)	97 (81.5%)
Unilateral pneumonia	14 (22.6%)	8 (14.0%)	22 (18.5%)
Oxygen requirements at admission (FAS)			
None	49 (79.0%)	40 (69.0%)	89 (74.2%)
Low flow O_2	13 (21.0%)	18 (31.0%)	31 (25.8%)

Concomitant medications (Safety population)			
Enoxaparin	42 (67.7%)	32 (57.1%)	74 (62.7%)
Dexamethasone	13 (21.0%)	6 (10.7%)	19 (16.1%)
Methylprednisolone	1 (1.6%)	1 (1.8%)	2 (1.7%)
Azithromycin	5 (8.1%)	6 (10.7%)	11 (9.3%)
Chloroquine	4 (6.5%)	6 (10.7%)	10 (8.5%)
Remdesivir	4 (6.5%)	6 (10.7%)	10 (8.5%)
Lopinavir/Ritonavir	3 (4.8%)	4 (7.1%)	7 (5.9%)
Tocilizumab	1 (1.6%)	0 (0.0%)	1 (0.8%)
Adverse Events (Safety population)			
Any adverse event	21 (33.9%)	20 (35.7%)	41 (34.7%)
Any severe adverse event	3 (4.8%)	2 (3.6%)	5 (4.2%)
Any treatment-related adverse event	0 (0%)	0 (0%)	0 (0%)
Any treatment-related severe adverse event	0 (0%)	0 (0%)	0 (0%)
Mortality at day 30^{th} follow-up	0 (0%)	0 (0%)	0 (0%)
Mortality at day 90^{th} follow-up	1 (1.6%)	1 (1.8%)	2 (1.7%)