High-dose *versus* low-dose prednisolone in symptomatic patients with post-COVID-19 diffuse parenchymal lung abnormalities: an open-label, randomised trial (the COLDSTER trial)

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To the Editor:

In some patients, respiratory symptoms and imaging abnormalities persist after acute coronavirus disease 2019 (COVID-19) pneumonia [1–3]. Chest computed tomography (CT) scans generally show diffuse parenchymal lung abnormalities consistent with organising pneumonia [4]. It has been proposed that the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could act as a trigger to exalt the presence of pre-existing interstitial lung abnormalities encountered in the general population, especially in smokers. Previous observational studies reported improvement with glucocorticoids in symptomatic patients with post-COVID-19 diffuse parenchymal lung abnormalities (PC-DPLAS) [4–6]. A recent guideline recommended glucocorticoids for treating PC-DPLAS [3]. However, there are no randomised controlled trials on therapies for this condition.

We conducted an investigator-initiated, single-centre, open-label, parallel-group, randomised, superiority trial of two doses of prednisolone at our institute. After institute ethics committee approval and protocol registration (COLDSTER trial; clinicaltrials.gov identifier number NCT04657484), we included consecutive, consenting subjects aged ⩾18 years at 3–8 weeks from acute COVID-19 symptom onset, if they had 1) COVID-19 diagnosed by real-time reverse transcriptase PCR or COVID-19 antigen; 2) persistent dyspnoea (modified Medical Research Council (mMRC) score ⩾2) or resting hypoxaemia (oxygen saturation ⩽94%) or exertional desaturation (⩾4% fall in oxygen saturation on exercise) at screening; and 3) diffuse abnormalities involving ⩾20% of the lung parenchyma on semiquantitative assessment on thin-section (1.0 mm) CT. We excluded subjects with any of the following: 1) ongoing intensive care; 2) pre-existing structural lung disease; 3) pregnancy or lactation; and 4) contraindication for prednisolone.

We allocated subjects 1:1 by computer-generated simple randomisation (allocation concealment in consecutively numbered sealed opaque envelopes) to receive either high-dose prednisolone (40 mg·day^{-1} for 1 week, followed by 30 mg·day^{-1} for 1 week, 20 mg·day^{-1} for 2 weeks and 10 mg·day^{-1} for 2 weeks) or low-dose prednisolone (10 mg·day^{-1} for 6 weeks). We assessed the resting oxygen saturation, dyspnoea severity (mMRC scale) and 6-min walk test (6MWT) at randomisation. We monitored for treatment compliance and adverse effects by telephone at 2 and 4 weeks. At 6 weeks, we performed the following assessments: resting oxygen saturation, dyspnoea severity (mMRC scale and Functional Assessment of Chronic Illness Therapy 10-item dyspnoea questionnaire), 6MWT, spirometry, thin-section chest CT, respiratory health status (King's Brief Interstitial Lung Disease Questionnaire), health-related quality of life (HRQoL) using the short-form 36-item questionnaire, treatment compliance and treatment-related adverse effects [7–11]. We assessed the radiological response both by scoring for resolution of overall diffuse lung abnormalities and a systematic semiquantitative scoring for individual radiological abnormalities (table 1) [12, 13].

We evaluated all outcomes 6 weeks after randomisation. The primary outcome was the proportion of subjects with a complete radiological response (⩾90% reduction in diffuse lung abnormalities) on CT.

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High-dose prednisolone may not be superior to a low-dose 6-week regimen in improving clinical, physiological and radiological outcomes, or health-related quality of life, in patients with symptomatic post-COVID-19 diffuse parenchymal lung abnormalities https://bit.ly/32zqnXt

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TABLE 1 Study outcomes assessed at 6 weeks

	High-dose prednisolone	Low-dose prednisolone	Mean difference (95% CI)	p-value
Patients, n	65	65		
Primary outcome				
Complete radiological response[#]	16 (24.6)	12 (18.5)	−0.06 (−0.20–0.08)	0.39
Key secondary outcomes				
Complete/good radiological response[#]	55 (84.6)	52 (80.0)	−0.05 (−0.18–0.09)	0.49
FVC, % predicted[¶]	71.1±16.3	67.4±14.8	−3.7 (−9.4–2.0)	0.21
Improvement in resting S_{pO_2},[+] %	2 (0–6)	2 (1–6)		0.91
Improvement in dyspnoea, mMRC score[+]	1 (1–2)	2 (1–2)		0.52
⩾1 point improvement[+]	56 (91.8)	56 (93.3)	0.02 (−0.09–0.12)	1.00
Other secondary outcomes				
Good composite response[#]	10 (15.4)	10 (15.4)	0 (−0.13–0.13)	1.00
Oxygen desaturation on exercise[+]	30 (52.6)	30 (50.8)	−0.02 (−0.19–0.16)	0.85
Score on the FACIT-Dyspnea scale[+]	45.5±11.4	43.3±9.8	−2.2 (−6.0–1.6)	0.25
K-BILD total score[+]	65.6±13.7	64.9±15.6	−0.7 (−5.9–4.6)	0.79
Short form-36 component scores[+]				
Physical functioning	59.4±26.3	62.9±28.5	3.5 (−6.4–13.4)	0.49
Role limitation – physical	61.5±23.1	58.3±27.9	−3.2 (−12.4–6.0)	0.50
Role limitation – emotional	74.9±30.8	69.4±35.9	−5.5 (−17.5–6.5)	0.38
Vitality	59.7±18.1	59.6±20.9	−0.1 (−7.1–6.9)	0.98
Mental health	71.8±17.7	68.6±19.6	−3.2 (−9.9–3.5)	0.35
Social functioning	76.4±25.4	69.2±29.9	−7.2 (−17.2–2.8)	0.15
Bodily pain	75.9±22.0	72.5±25.8	−3.4 (−12.0–5.2)	0.43
General health	63.9±18.7	61.6±19.9	−2.3 (−9.3–4.7)	0.51
Exploratory outcomes				
6MWD,[§] m	349±93	318±129	−31.0 (−71.4–9.4)	0.15
Improvement in 6MWD,[f] m	86 (33–128)	70 (43–170)		0.55
Change in chest CT scores[+,##]				
Ground-glass opacities	−1.01±1.63	−0.53±1.45	0.48 (−0.08–1.04)	0.09
Consolidation	−1.16±0.88	−1.13±1.10	0.03 (−0.33–0.39)	0.88
Reticulation	−0.08±0.85	−0.02±0.80	0.06 (−0.24–0.36)	0.71
Parenchymal bands	0.14±0.77	0.28±0.87	0.14 (−0.16–0.44)	0.35
Traction bronchiectasis	0.36±1.13	0.37±1.22	0.01 (−0.41–0.43)	0.98
Adverse effects[#]				
Any	46 (70.8)	50 (76.9)	0.06 (−0.09–0.21)	0.55
Hyperglycaemia	21 (32.3)	19 (29.2)	−0.03 (−0.19–0.13)	0.20
Hypertension	15 (23.1)	14 (21.5)	−0.02 (−0.16–0.13)	0.83
Cushingoid habitus	13 (20.0)	13 (20.0)	0 (−0.13–0.13)	1.00
Fatigue	9 (13.8)	13 (20.0)	0.06 (−0.07–0.19)	0.48
Weight gain (>10% of baseline)	4 (6.2)	5 (7.7)	0.02 (−0.08–0.11)	1.00
Dyspepsia	3 (4.6)	7 (10.8)	0.06 (−0.04–0.16)	0.19
Others[¶¶]	19 (29.2)	27 (41.5)	0.12 (−0.04–0.28)	0.20

Data are presented as n (%), mean±SD or median (interquartile range), unless otherwise stated. FVC: forced vital capacity; S_{pO_2}; peripheral oxygen saturation; mMRC: modified Medical Research Council; FACIT: Functional Assessment of Chronic Illness Therapy; K-BILD: King's Brief Interstitial Lung Disease; 6MWD: 6-min walk distance; CT: computed tomography. [#]: outcomes presented for all subjects (n=65 in each group) with the worse outcomes assumed for those who were lost to follow-up; [¶]: 59 subjects in the high-dose group and 57 in the low-dose group were able to perform spirometry; [+]: outcomes reported for patients who completed follow-up (high-dose group n=61, low-dose group n=60); [§]: 57 and 59 subjects could perform the 6-min walk test (6MWT) at 6 weeks in the high-dose and low-dose groups, respectively; [f]: paired data available for 6MWT for 44 (high-dose group) and 37 (low-dose group) subjects; [##]: ground-glass opacities, consolidation, reticulation and parenchymal bands were scored semi-quantitatively in each lobe (right upper lobe, right middle lobe, right lower lobe, left upper lobe/lingula and left lower lobe) on chest CT. A score of 0 indicates no involvement, 1 represents <5% of lobe involved (present but minimal), 2 reflects 5–25%, 3 indicates 25–49%, 4 signifies 50–75% and 5 denotes >75% involvement. For each feature, the lobe scores were summed and divided by five to obtain an average (scale of 0–5), indicating the proportion of the total lung parenchyma showing the feature. Traction bronchiectasis was scored as absent (0) or present (1) for each lobe. The total score for traction bronchiectasis was calculated by summing up the respective scores for the five lobes; [¶¶]: other adverse effects (rarer events with <10 events in the study population) included skin thinning and bruising, insomnia, muscular weakness, mood changes, abdominal pain, infection, headache, visual disturbance, dysgeusia, hypertrichosis and acne.

The key secondary outcomes included the proportion of subjects with a complete or good radiological response (⩾50% resolution in diffuse lung abnormalities), percentage of predicted forced vital capacity (FVC), improvements in the resting oxygen saturation and dyspnoea severity and adverse effects.

Between December 2020 and June 2021, we screened 290 subjects and randomised 65 to each group. The major reasons for exclusion were mild lung abnormalities (n=82), contraindications to prednisolone (n=27), consent refusal (n=23) and others (n=28). The study groups had similar baseline characteristics with a mean age of 57 years, 32% women and 73% subjects with at least one comorbidity. All subjects were hospitalised for acute COVID-19 illness. Approximately 98% had either critical or severe disease according to World Health Organization criteria; 43% received either mechanical ventilation or high-flow nasal oxygen. Most (76%) subjects were randomised after hospital discharge (median of 36 days from acute COVID-19 symptom onset and 15 days since hospital discharge). At randomisation, the subjects had a median mMRC dyspnoea score of 3; 88% of subjects had exertional (or resting) hypoxaemia with 27% requiring supplemental oxygen. Approximately 91% had an organising pneumonia pattern on chest CT. The cumulative glucocorticoid dose received during acute COVID-19 management (median dose, 505 mg prednisolone equivalent) was similar between the study groups (p=0.16).

61 (93.8%) and 60 (92.3%) subjects completed 6 weeks' follow-up in the high-dose and low-dose groups, respectively (compliance by cumulative dose, 96.8% and 96.2%, respectively). We found a complete radiological response in 16 (24.6%) and 12 (18.5%) subjects in the high-dose and low-dose groups, respectively (p=0.39). 55 (84.6%) and 52 (80.0%) subjects had a complete or good radiological response in the respective groups (p=0.49). The mean FVC at 6 weeks was similar (high dose 71.1% pred, low dose 67.4% pred; p=0.21). The median (interquartile range) improvements in resting oxygen saturation (high dose 2 (0–6), low-dose 2 (1–6); p=0.91) and mMRC scale (high dose 1 (1–2), low-dose 2 (1–2); p=0.52) were similar. Only one subject (high-dose group) required supplemental oxygen at 6 weeks. In addition, the other secondary and exploratory outcomes did not differ between the study groups (table 1). The outcomes did not differ by study group allocation in any of the analysed subgroups based on age (<60 years *versus* ⩾60 years), sex, comorbidity (none *versus* any), body weight (<80 kg *versus* ⩾80 kg), duration since COVID-19 onset (⩽4 weeks *versus* >4 weeks), cumulative prednisolone dose before randomisation (<500 mg *versus* ⩾500 mg), peak oxygen requirement during hospitalisation (fraction of inspired oxygen ⩽0.5 *versus* >0.5), mechanical ventilation and dyspnoea severity (mMRC grade ⩽2 *versus* grade 3 or 4).

The incidence of treatment-related adverse effects was similar between the study groups (table 1). There were no deaths. Four infections occurred (pulmonary tuberculosis, tracheostomy site infection, recurrent symptomatic acute COVID-19 in the high-dose group and an uncomplicated urinary tract infection in the low-dose group); all responded to appropriate treatment.

To our knowledge, this is the first randomised trial of any therapy for PC-DPLAS. A complete radiological response was achieved in only 21% of subjects; this proportion lies in the higher range of early imaging outcomes previously reported in PC-DPLAS [13–15]. Dyspnoea was reduced by the minimal clinically important difference (⩾1 mMRC point) in 92% of subjects, similar between the study groups. We also found significant improvements in oxygen saturation and 6-min walk distance in both groups. However, glucocorticoid therapy was not without harm: 74% of subjects developed at least one adverse effect. Even in the low-dose group, ∼29% and ∼22% of patients developed hyperglycaemia and hypertension, respectively.

The management of PC-DPLAS remains unclear. Many physicians adopt a "wait-and-see" approach, administering glucocorticoids, if anything, to patients whose symptoms or hypoxaemia persist beyond several weeks to months [4, 6]. In contrast, several physicians prescribe prolonged high-dose glucocorticoids early in the course of PC-DPLAS [5]. Segala *et al*. [6] treated 10 patients with persistent respiratory failure beyond 3 weeks after acute COVID-19 symptom onset with high-dose intravenous methylprednisolone and observed significant improvements in oxygenation. Myall *et al*. [4] treated 30 patients with persistent symptoms and a radiological organising pneumonia pattern with medium-dose prednisolone an average of 11 weeks after symptom onset and reported a significant clinicophysiological response. We administered prednisolone at an average of 5 weeks from acute COVID-19 symptom onset (∼2 weeks from discharge) to patients with PC-DPLAS with considerable ongoing symptoms, oxygenation defects and significant residual radiological abnormalities. We observed similar improvement as previous studies, even with low-dose prednisolone [4, 6].

An important limitation of the study is the lack of a placebo arm. Nevertheless, we did our best to exclude patients with only mild PC-DPLAS. Our inclusion criteria, significant exclusion rate and the baseline radiological and physiological characteristics of our study subjects reflect our attempts to include only patients with persistent and severe PC-DPLAS. Yet, our study cannot answer whether glucocorticoids are required at all for treating PC-DPLAS. It is plausible that our subjects, although significantly symptomatic,

could have improved spontaneously without any glucocorticoid therapy. However, our study does indicate that a lower glucocorticoid dose may be sufficient once a decision is made to treat persistent PC-DPLAS. Other limitations include the single-study centre, small sample size, short follow-up and unavailability of other pulmonary function tests such as diffusion capacity of the lung.

In conclusion, we did not find high-dose prednisolone better than low-dose prednisolone in improving the clinical, radiological, physiological and HRQoL outcomes in PC-DPLAS. A placebo-controlled trial of glucocorticoids is required to better inform clinical practice for treating PC-DPLAS.

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This trial was prospectively registered at ClinicalTrials.gov with identifier NCT04657484. Data collected for the study, including deidentified participant data and related documents, including the protocol, statistical analysis plan and informed consent form, will be made available to qualified researchers after publication of the manuscript upon reasonable request *via* application to the corresponding author.

Conflict of interest: None declared.

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