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Early View

Research letter

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

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

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TAKE HOME MESSAGE

High-dose prednisolone may not be superior to a low-dose regimen given over 6 weeks in improving the clinical, physiologic, and radiologic outcomes, or the health-related quality of life in symptomatic post-COVID-19 diffuse parenchymal lung abnormalities.

In some patients, respiratory symptoms and imaging abnormalities persist after acute coronavirus disease 2019 (COVID-19) pneumonia.[1-3] The chest computed tomography (CT) generally shows diffuse parenchymal lung abnormalities consistent with organising pneumonia (OP).[4] It has also been proposed that the novel 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; NCT04657484), we included consecutive, consenting subjects aged ≥18 years at 3-8 weeks from acute COVID-19 symptom onset, if they had: (i) COVID-19 diagnosed by real-time reverse transcriptase polymerase chain reaction or COVID-19 antigen; (ii) persistent dyspnoea (modified Medical Research Council scale [mMRC] ≥2), or resting hypoxaemia (oxygen saturation ≤94%), or exertional desaturation (≥4% fall in oxygen saturation on exercise) at screening; and, (iii) 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: (i) ongoing intensive care; (ii) pre-existing structural lung disease; (iii) pregnancy or lactation; and (iv) 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 (40 mg/day for one week, followed by 30 mg/day for one week, 20 mg/day for two weeks, and 10 mg/day for two weeks) or low-dose (10 mg/day of prednisolone for six weeks) prednisolone. We assessed the resting oxygen saturation, dyspnoea severity (mMRC scale), and six-minute walk test (6MWT) at randomisation. We monitored for treatment compliance and adverse effects telephonically at two and four weeks. At six 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 CT chest, respiratory health status (King's brief ILD questionnaire), health-related quality of life (HRQoL) using short-form 36 (SF-36) questionnaire, treatment compliance, and treatment-related adverse effects [7-11] We assessed the radiologic response both by scoring for resolution of overall diffuse lung abnormalities and a systematic semiquantitative scoring for individual radiologic abnormalities (Table 1 legend).[12, 13]

We evaluated all outcomes six weeks after randomisation. The primary outcome was the proportion of subjects with a complete radiologic response (≥90% reduction in diffuse lung abnormalities) on CT. The key secondary outcomes included the proportion of subjects with a complete or good radiologic response (≥50% resolution in diffuse lung abnormalities), percentage of the 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. About 98% had either critical or severe disease according to the World Health Organization criteria; 43% received either mechanical ventilation or high-flow nasal oxygen. Most (76.2%) 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) hypoxemia with 27% requiring supplemental oxygen. About 91% had OP pattern on CT chest. 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).

Sixty-one (93.8%) and 60 (92.3%) subjects completed six-week follow-up in the high-dose and low-dose groups, respectively (compliance by cumulative dose, 96.8% and 96.2%). We found a complete radiologic response in 16 (24.6%) and 12 (18.5%) subjects in the high-dose and low-dose groups, respectively (p=0.39). Fifty-five (84.6%) and 52 (80.0%) subjects had a complete or good radiologic response in the respective groups (p=0.49). The mean percentage-predicted FVC at six weeks was similar (high-dose: 71.1, low-dose: 67.4; 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 six weeks. The other secondary

and exploratory outcomes also 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 vs. ≥60 years), sex, comorbidity (none vs. any), body weight (<80 kg vs. ≥80 kg), duration since COVID-19 onset (four weeks or less vs. more than four weeks), cumulative prednisolone dose before randomization (<500 mg vs. ≥500 mg), peak oxygen requirement during hospitalisation (fraction of inspired oxygen ≤0.5 vs. >0.5), mechanical ventilation, and dyspnoea severity (mMRC grade 2 or less vs. 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, 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 radiologic 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 the six-minute walk distance in both the groups. Glucocorticoid therapy was, however, not without harm; 74% of subjects developed at least one adverse effect. Even in the low-dose group, about 29% and 22% patients developed hyperglycaemia and hypertension, respectively.

The management of PC-DPLAS remains unclear. Many physicians adopt a 'wait-and-see' approach, administering glucocorticoids, if at all, to patients whose symptoms or hypoxaemia persist beyond several weeks to months.[4, 6] Contrarily, several physicians prescribe prolonged high-dose glucocorticoids early in the course of PC-DPLAS.[5] Previously, Segala et al. treated 10 patients with persistent respiratory failure beyond three weeks after acute COVID-19 symptom onset with high-dose intravenous methylprednisolone and observed significant improvements in oxygenation.[6] Myall et al. treated 30 patients with persistent symptoms and a radiologic OP pattern with medium-dose prednisolone an average of 11 weeks after symptom onset and reported significant clinico-physiologic response.[4] We administered prednisolone at an average of five weeks from acute COVID-19 symptom onset (about two weeks from discharge) to patients with PC-DPLAS with considerable ongoing symptoms, oxygenation defects, and significant residual radiologic 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 attempted our best to exclude patients with only mild PC-DPLAS. Our inclusion criteria, our significant exclusion rate, and the baseline radiologic and physiologic characteristics of our study subjects reflect our attempts to include only patients with persistent and severe PC-DPLAS. Yet, our study cannot answer the question of 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 a single study centre, small sample size, short follow-up, and unavailability of other pulmonary function tests such as diffusion capacity.

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

Table 1. Study outcomes assessed at six weeks

	High-dose prednisolone (n=65)	Low-dose prednisolone (n=65)	Mean difference (95% confidence intervals)	P value
Primary outcome				
Complete radiologic response[1]	16 (24.6)	12 (18.5)	-0.06 (-0.20, 0.08)	0.39
Key secondary outcomes				
Complete/good radiologic response[1]	55 (84.6)	52 (80.0)	-0.05 (-0.18, 0.09)	0.49
Forced vital capacity, %predicted[2]	71.1 ± 16.3	67.4 ± 14.8	-3.7 (-9.4, 2.0)	0.21
Improvement in resting SpO_2[3], %	2 (0-6)	2 (1-6)		0.91
Improvement in dyspnoea, mMRC[3]	1 (1-2)	2 (1-2)		0.52
≥1 point improvement[3], n (%)	56 (91.8)	56 (93.3)	0.02 (-0.09, 0.12)	1.00
Other secondary outcomes				
Good composite response[1]	10 (15.4)	10 (15.4)	0 (-0.13, 0.13)	1.00
Oxygen desaturation on exercise[3]	30 (52.6)	30 (50.8)	-0.02 (-0.19, 0.16)	0.85
Score on the FACIT-Dyspnea scale[3]	45.5 ± 11.4	43.3 ± 9.8	-2.2 (-6.0, 1.6)	0.25
K-BILD total score[3]	65.6 ± 13.7	64.9 ± 15.6	-0.7 (-5.9, 4.6)	0.79
Short form-36 component scores[3]				
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				
Six-minute walk distance,[4] meters	349 ± 93	318 ± 129	-31.0 (71.4, 9.4)	0.15
Improvement in 6MWD,[5] meters	86 (33-128)	70 (43-170)		0.55
Change in chest CT scores[3,6]				
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,[1] n (%)				
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[7]	19 (29.2)	27 (41.5)	0.12 (-0.04, 0.28)	0.20

6MWD-six-minute walk distance, CT-computed tomography, FACIT-Functional Assessment of Chronic Illness Therapy, FLT-functional limitation, K-BILD-King's Brief Interstitial Lung Disease, mMRC-modified Medical Research Council, SpO_2-oxygen saturation

The values represent either mean ± standard deviation or median (interquartile range), unless otherwise specified.

[1]Outcomes presented for all subjects (65 in each group) with the worse outcomes assumed for those who were lost to follow up.

[2]59 subjects in the high-dose group and 57 in the low-dose group could perform spirometry.

[3]Outcomes reported for patients who completed follow-up (high-dose group: 61, low-dose group: 60).

[4]57 and 59 subjects could perform the six-minute walk test at six weeks in the high-dose and low-dose groups, respectively.

[5]Paired data available for six-minute walk test for 44 (high-dose group) and 37 (low-dose group) subjects.

[6]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 CT chest. 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 5 to obtain an average (scale of 0 to 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.

[7]Other adverse effects (rarer events with less than 10 events in both the groups) included skin thinning and bruising, insomnia, muscular weakness, mood changes, abdominal pain, infection, headache, visual disturbance, dysgeusia, hypertrichosis, and acne.

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