Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

An open-label randomized, controlled trial of the effect of lopinavir and ritonavir, lopinavir and ritonavir plus interferon-β-1a, and hydroxychloroquine in hospitalized patients with COVID-19: final results

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To the Editor,

We published in the December 2021 issue of *Clinical Microbiology and Infection* the preliminary results of the DisCoVeRy trial regarding the efficacy of lopinavir/ritonavir, lopinavir/ritonavir plus interferon (IFN)-β-1a, and hydroxychloroquine in hospitalized patients with COVID-19 [1]. These three experimental repurposed treatments did not show clinical or virological benefit in the studied population. Of note, the number of patients included was low as inclusion in those arms of the trial was prematurely stopped by the data safety monitoring board (DSMB). Here, after completion of data monitoring, we report the final analysis, including two secondary endpoints which were not previously reported.

Briefly, the DisCoVeRy trial is a phase 3 open-label randomized, controlled trial evaluating the efficacy and safety of repurposed drugs in adults hospitalized for COVID-19, sponsored by Inserm (NCT04315948). The trial was approved by the Ethics Committee (CPP Ile-de-France-III, approval #20.03.06.51,744). Eligible participants were adults (aged ≥18 years) hospitalized with a PCR-positive (<72 hours) severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and pulmonary rales or crackles with a peripheral oxygen saturation ≤94% or requiring supplemental oxygen. The primary endpoint was the clinical status at day 15 as measured on the following 7-point ordinal scale of the WHO Master Protocol (version 3.0, March 3, 2020), analyzed using a proportional odds model: (1) not hospitalized, no limitation on activities; (2) not hospitalized, limitation on activities; (3) hospitalized, not requiring supplemental oxygen; (4) hospitalized, requiring supplemental oxygen; (5) hospitalized, on non-invasive ventilation or high flow oxygen devices; (6) hospitalized, on invasive mechanical ventilation or Extracorporeal membrane oxygenation (ECMO); and (7) death. Full details on the trial design are available in [1].

In the final dataset, 603 participants were randomized and 593 were evaluable for analysis—control arm ($n = 149$), lopinavir and ritonavir arm ($n = 147$), lopinavir and ritonavir plus IFN-ß-1a arm ($n = 147$), and hydroxychloroquine arm ($n = 150$). Regarding the primary endpoint, the final adjusted OR (aOR) for clinical improvement using the 7-point ordinal scale at day 15 were not in favour of experimental treatments—lopinavir and ritonavir vs. control, aOR 0.82 (95% CI, 0.54–1.25); lopinavir and ritonavir plus IFN-ß-1a vs. control, aOR 0.69 (95% CI, 0.45–1.05); hydroxychloroquine vs. control, aOR 0.94 (95% CI, 0.62–1.41) (Table 1). Some modifications were observed regarding the secondary outcomes; full results are available elsewhere [2]. In-hospital mortality was not affected by any treatment arm (Table 1). Three-month mortality was significantly higher for participants assigned to the lopinavir/ritonavir plus IFN-ß-1a arm than participants assigned to the control arm, while no difference was observed for the lopinavir/ritonavir and the hydroxychloroquine arms (Table 1). In addition, participants assigned to the lopinavir/ritonavir plus IFN-ß-1a had a significantly longer time to hospital discharge, either when considered as a single endpoint or as composite endpoints (Table 1).

The previously reported higher rate of participants experiencing any adverse event in the lopinavir/ritonavir plus IFN-ß-1a arm was no longer significant in the final dataset—control arm ($n = 113/149$, 75.8%), lopinavir/ritonavir plus IFN-ß-1a arm ($n = 122/145$, 84.1%; $p = 0.08$ vs. control); it remained significantly higher in the lopinavir and ritonavir arm ($n = 125/147$, 85.0%; $p = 0.05$ vs. control).

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Table 1
Primary and secondary outcomes for patients included in the DisCoVeRy trial for L/r, L/r plus IFN-β-1a, and HCQ, according to disease severity at baseline

	Overall ($N = 593$)		Control ($n = 149$)		L/r ($n = 147$)		L/r + IFN-ß-1a ($n = 147$)		HCQ ($n = 150$)		L/r vs. control effect measure (95% CI)	L/r + IFN-ß-1a vs. control effect measure (95% CI)	HCQ vs. control effect measure (95% CI)
	Moderate ($n = 379$)	Severe ($n = 214$)	Moderate ($n = 95$)	Severe ($n = 54$)	Moderate ($n = 95$)	Severe ($n = 52$)	Moderate ($n = 93$)	Severe ($n = 54$)	Moderate ($n = 96$)	Severe ($n = 54$)			
7-point ordinal scale at day 15, *n* (%)													
1. Not hospitalized, no limitations on activities	83 (21.9)	3 (1.4)	22 (23.2)	1 (1.9)	21 (22.1)	1 (1.9)	20 (21.5)	0 (0.0)	20 (20.8)	1 (1.9)	OR = 0.82 (0.54 to 1.25) [P = 0.36]	OR = 0.69 (0.45 to 1.05) [P = 0.08]	OR = 0.94 (0.62 to 1.41) [P = 0.76]
2. Not hospitalized, limitation on activities	155 (40.9)	16 (7.5)	44 (46.3)	6 (11.1)	37 (38.9)	2 (3.8)	37 (39.8)	1 (1.9)	37 (38.5)	7 (13.0)			
3. Hospitalized, not requiring supplemental oxygen	53 (14.0%)	25 (11.7%)	8 (8.4%)	5 (9.3%)	14 (14.7%)	6 (11.5%)	13 (14.0%)	6 (11.1%)	18 (18.8%)	8 (14.8%)			
4. Hospitalized, requiring supplemental oxygen	40 (10.6)	32 (15.0)	10 (10.5)	10 (18.5)	10 (10.5)	9 (17.3)	9 (9.7)	6 (11.1)	11 (11.5)	7 (13.0)			
5. Hospitalized, on non-invasive ventilation or high flow oxygen devices	6 (1.6%)	8 (3.7%)	1 (1.1%)	2 (3.7%)	2 (2.1%)	1 (1.9%)	2 (2.2%)	3 (5.6%)	1 (1.0%)	2 (3.7%)			
6. Hospitalized, on invasive mechanical ventilation or ECMO	27 (7.1)	107 (50.0)	6 (6.3)	24 (44.4)	8 (8.4)	29 (55.8)	8 (8.6)	28 (51.9)	5 (5.2)	26 (48.1)			
7. Death	15 (4.0)	23 (10.7)	4 (4.2)	6 (11.1)	3 (3.2)	4 (7.7)	4 (4.3)	10 (18.5)	4 (4.2)	3 (5.6)			
7-point ordinal scale at day 29, *n* (%)													
1. Not hospitalized, no limitations on activities	150 (39.6)	20 (9.3)	36 (37.9)	7 (13.0)	35 (36.8)	6 (11.5)	36 (38.7)	1 (1.9)	43 (44.8)	6 (11.1)	OR 0.95 (0.63 to 1.43) (p = 0.80	OR 0.80 (0.53 to 1.21) (p = 0.29)	OR 1.26 (0.84 to 1.90) (p = 0.27)
2. Not hospitalized, limitation on activities	135 (35.6)	34 (15.9)	35 (36.8)	5 (9.3)	39 (41.1)	8 (15.4)	31 (33.3)	9 (16.7)	30 (31.3)	12 (22.2)			
3. Hospitalized, not requiring supplemental oxygen	40 (10.6)	47 (22.0)	11 (11.6)	15 (27.8)	9 (9.5)	8 (15.4)	10 (10.8)	11 (20.4)	10 (10.4)	13 (24.1)			
4. Hospitalized, requiring supplemental oxygen	14 (3.7)	20 (9.3)	5 (5.3)	6 (11.1)	3 (3.2)	4 (7.7)	4 (4.3)	6 (11.1)	2 (2.1)	4 (7.4)			
5. Hospitalized, on non-invasive ventilation or high flow oxygen devices	5 (1.3)	7 (3.3)	1 (1.1)	1 (1.9)	2 (2.1)	2 (3.8)	1 (1.1)	1 (1.9)	1 (1.0)	3 (5.6)			
6. Hospitalized, on invasive mechanical ventilation or ECMO	14 (3.7)	50 (23.4)	2 (2.1)	12 (22.2)	3 (3.2)	14 (26.9)	5 (5.4)	13 (24.1)	4 (4.2)	11 (20.4)			
7. Death	21 (5.5)	36 (16.8)	5 (5.3)	8 (14.8)	4 (4.2)	10 (19.2)	6 (6.5)	13 (24.1)	6 (6.3)	5 (9.3)			

Time to improvement of 2 categories of the 7-point ordinal scale or hospital discharge within day 29, d, median (IQR)	10 (7−17)	21 (13−29)	9 (6−14)	18 (10−29)	12 (8−17)	28 (14−29)	11 (8−19)	29 (1629)	10 (7−19)	18 (12−29)	HR 0.70 (0.54 to 0.92) (p = 0.01)	HR 0.68 (0.52 to 0.89) (p = 0.008)	HR 0.79 (0.61 to 1.03) (p = 0.09)
Time to National Early Warning Score ≤2 or hospital discharge within 29 days, d, median (IQR)	9 (5−16)	29 (19−29)	8 (5−14)	29 (19−29)	10 (6−16)	29 (21−29)	10 (6−18)	29 (29−29)	9 (5−15)	29 (16−29)	HR 0.84 (0.64 to 1.10) (p = 0.21)	HR 0.72 (0.54 to 0.96) (p = 0.02)	HR 0.93 (0.71 to 1.23) (p = 0.63)
Time to hospital discharge within 29 days, d, median (IQR)	11 (7−21)	29 (22−29)	9 (6−16)	29 (19−29)	12 (8−21)	29 (23−29)	11 (8−26)	29 (29−29)	11 (8−21)	29 (17−29)	HR 0.81 (0.61 to 1.08) (p = 0.15)	HR 0.72 (0.54 to 0.97) (p = 0.03)	HR 0.84 (0.63 to 1.12) (p = 0.24)
Oxygenation-free days until day 29, d, median (IQR)	22 (15−25)	0 (0−13)	22 (15−25)	4 (0−14)	22 (15−25)	0 (0−13)	22 (15−25)	0 (0−7)	22 (17−25)	5 (0−15)	LSMD = -0.99 (-2.92 to 0.95) (p = 0.32)	LSMD = -1.70 (-3.63 to 0.24) (p = 0.09)	LSMD = 0.06 (-1.89 to 2.01) (p = 0.95)
Ventilator-free days until day 29, d, median (IQR)	29 (29−29)	11 (0−20)	29 (29−29)	13 (0−22)	29 (29−29)	5 (0−20)	29 (29−29)	4 (0−16)	29 (29−29)	14 (1−22)	LSMD = -0.75 (-2.72 to 1.22) (p = 0.46)	LSMD = -2.07 (-4.08 to -0.05) (p = 0.05)	LSM D = 0.35 (-1.64 to 2.34) (p = 0.73)
In-hospital mortality, *n* (%)	20 (5.3)	36 (16.8)	5 (5.3)	8 (14.8)	4 (4.2)	10 (19.2)	5 (5.4)	13 (24.1)	6 (6.3)	5 (9.3)	OR 1.12 (0.50 to 2.51) (p = 0.70)	OR 1.47 (0.68 to 3.18) (p = 0.32)	OR 0.89 (0.36 to 1.92) (p = 0.66)
Death within 28 days, *n* (%)	20 (5.3)	36 (16.8)	5 (5.3)	8 (14.8)	4 (4.2)	10 (19.2)	5 (5.4)	13 (24.1)	6 (6.3)	5 (9.3)	OR 1.12 (0.50 to 2.51) (p = 0.70)	OR 1.47 (0.68 to 3.18) (p = 0.32)	OR 0.89 (0.36 to 1.92) (p = 0.66)
Death within 90 days, *n* (%)	23 (6.1)	46 (21.5)	5 (5.3)	8 (14.8)	5 (5.3)	12 (23.1)	7 (7.5)	17 (31.5)	6 (6.3)	9 (16.7)	OR 1.41 (0.65 to 3.06) (p = 0.39)	OR 2.11 (1.01 to 4.39) (p = 0.04)	OR 1.17 (0.53 to 2.58) (p = 0.70)

Analyses were stratified on the disease severity at baseline (moderate: 7-point ordinal scale 3 or 4; severe: 7-point ordinal scale 5 or 6), and adjusted effect measures are reported in the table. Abbreviations: ECMO, Extra-corporeal membrane oxygenation; HCQ, hydroxychloroquine; HR, hazard ratio; IFN, interferon; IQR, interquartile range; LRT, L/r, Lopinavir/ritonavir; lower respiratory tract; LSMD, least-square mean difference; NP, nasopharyngeal.

Regarding the reporting of any serious adverse event, the proportion remained significantly higher in both lopinavir and ritonavir-containing arms than in the control arm—control arm (n = 58/149, 38.9%), lopinavir and ritonavir arm (n = 76/147, 51.7%; p = 0.02 vs. control), lopinavir/ritonavir plus IFN-ß-1a arm (n = 80/145, 55.2%; p = 0.01 vs. control). No significant difference was observed regarding safety data in the hydroxychloroquine arm.

Overall, the final results of the DisCoVeRy trial for the efficacy and safety of lopinavir/ritonavir, lopinavir/ritonavir plus IFN-β-1a, and hydroxychloroquine confirm what was observed in the preliminary report. They support recommendations against the use of hydroxychloroquine and lopinavir and ritonavir in hospitalized patients with COVID-19. The results of the lopinavir and ritonavir plus IFN-ß-1a arm raise interesting questions. Indeed, because defects in IFN signaling pathways have been shown to be associated with severe COVID-19 [3], one could assume that IFN treatment might improve COVID-19 clinical outcome. Here, results suggest a detrimental effect of IFN-ß-1a treatment—participants assigned to the lopinavir and ritonavir plus IFN-β-1a arm had significantly longer time to hospital discharge (alone or combined in composite endpoints) and higher 90-day mortality than untreated controls, whereas these outcomes were not significantly different between participants assigned to lopinavir/ritonavir alone or to the control arm. Overall, this suggests that IFN-ß-1a administration is not always appropriate, and that screening of IFN signalling pathways may be required to identify patients who would most benefit from IFN treatment [4].

Transparency declaration

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Appendix A. Supplementary data

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References

[1] Ader F, Peiffer-Smadja N, Poissy J, Bouscambert-Duchamp M, Belhadi D, Diallo A, et al. An open-label randomized controlled trial of the effect of lopinavir/ritonavir, lopinavir/ritonavir plus IFN-β-1a and hydroxychloroquine in hospitalized patients with COVID-19. Clin Microbiol Infect 2021;27:1826–37. https://doi.org/10.1016/j.cmi.2021.05.020.

[2] Ader F, Peiffer-Smadja N, Poissy J, Bouscambert-Duchamp M, Belhadi D, Diallo A, et al. An open-label randomized, controlled trial of the effect of lopinavir/ritonavir, lopinavir/ritonavir plus IFN-beta-1a and hydroxychloroquine in hospitalized patients with COVID-19— inal results from the DisCoVeRy trial. Infectious Diseases (except HIV/AIDS); 2022. https://doi.org/10.1101/2022.02.16.22271064.

[3] Hadjadj J, Yatim N, Barnabei L, Corneau A, Boussier J, Smith N, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. Science 2020;369:718–24. https://doi.org/10.1126/science.abc6027.

[4] Galbraith MD, Kinning KT, Sullivan KD, Araya P, Smith KP, Granrath RE, et al. Specialized interferon action in COVID-19. Proc Natl Acad Sci USA 2022;119:e2116730119. https://doi.org/10.1073/pnas.2116730119.