Dexamethasone for COVID-19 – Preliminary Report

Effect of Dexamethasone in Hospitalized Patients with COVID-19 Preliminary Report

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Background

- Amongst COVID-19 patients admitted to UK hospitals:
  - Overall CFR > 26%
  - CFR > 37% in patients requiring invasive mechanical ventilation (ivm)
    - Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. Bmj 2020; 369: m1985

- Host Immune response thought to play a key role
- On autopsy: diffuse alveolar damage, inflammatory infiltrates and microvascular thrombosis

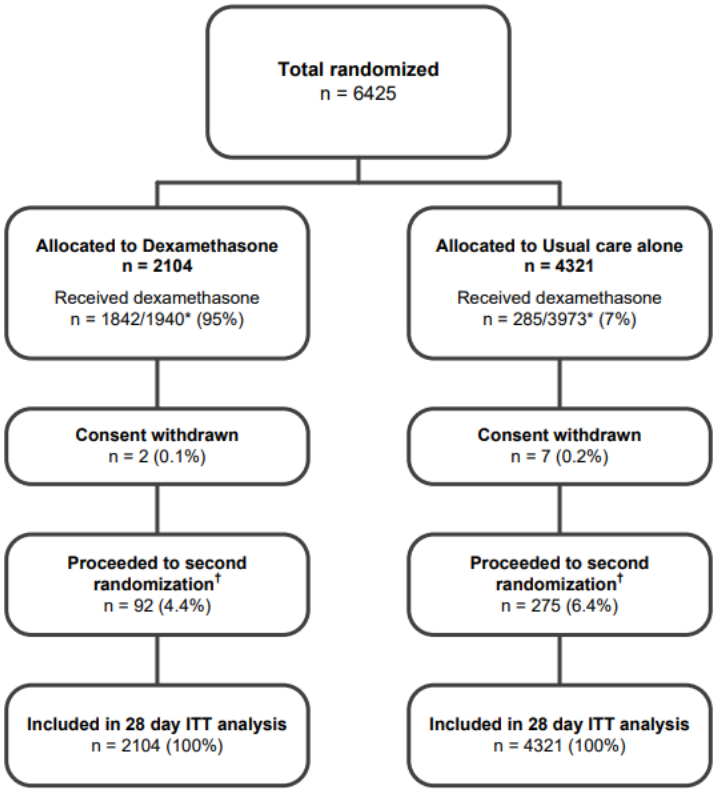
- Value of corticosteroids widely debated

  - Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med*. Published online March 13, 2020.
  - Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020; 395(10223): 473-5

Aim/Methods

- Aim of the RECOVERY Trial:
  - Evaluate the effects of potential treatments in patients hospitalized with COVID-19

  - Investigator-initiated, individually randomized, controlled, open-label adaptive platform trial
  - 176 NHS hospital organizations in the UK
  - Coordinated by Nuffield Dep. Of population Health at Univ. of Oxford



ITT – intention to treat
* 1940/2104 (92.1%) and 3973/4321 (91.9%) patients have a completed follow-up form at time of analysis.
† Randomization to Tocilizumab vs. No additional treatment in accordance with protocol version 4.0 or later. In addition, 14 patients were additionally randomized to convalescent plasma vs control (5 [0.2%] patients allocated to dexamethasone arm vs 9 [0.2%] patients allocated to usual care) in accordance with protocol V6.0.

- Eligible
  - Clinically suspected or laboratory confirmed Sars-Cov 2 infection
  - No medical history that might put the patient at significant risk in the opinion of the attending clinician
  - Initially at least 18 years, from may 9th age limit removed
- Randomization
  - Web-based case report form incl. demographics, respiratory support, major comorbidities
  - Assigned in a 2:1 ratio either to usual standard of care plus dexamethasone 6mg once daily for up to 10 days (web-based simple allocation)
  - Patients for whom dexamthasone was either unavailable or considered definitely indicated/contraindicated by managing doctor were excluded from entry in randomization

Outcome

- **Primary Outcome**
  - All-cause mortality within 28 days of randomization

- **Secondary Outcome**
  - Time to discharge from hospital (when not receiving IMV)
  - Subsequent receipt of invasive mechanical ventilation (IVM) or death

- **Pre-specified analyses of the primary outcome were performed in 5 subgroups defined by characteristics**
  - Age
  - Sex
  - Level of respiratory support
  - Days since symptoms onset
  - Predicted 28-day mortality risk

- **Sample size estimate**
  - If 28-day mortality was 20%, a comparison of 2000 patient with active drug vs 4000 patients with usual care would yield 90% power to detect a clinically relevant difference

Table 1: Baseline characteristics by randomized allocation and level of respiratory support received

	Treatment allocation		Respiratory support received at randomization		
	Dexamethasone (n=2104)	Usual care (n=4321)	No oxygen received (n=1535)	Oxygen only (n=3883)	Invasive mechanical ventilation (n=1007)
Age, years	66.9 (15.4)	65.8 (15.8)	69.3 (17.6)	66.7 (15.3)	59.0 (11.5)
<70	1142 (54%)	2506 (58%)	660 (43%)	2149 (55%)	839 (83%)
≥70 to <80	467 (22%)	860 (20%)	338 (22%)	837 (22%)	152 (15%)
≥80	495 (24%)	955 (22%)	537 (35%)	897 (23%)	16 (2%)
Sex					
Male	1338 (64%)	2750 (64%)	892 (58%)	2462 (63%)	734 (73%)
Female*	766 (36%)	1571 (36%)	643 (42%)	1421 (37%)	273 (27%)
Number of days since symptom onset	8 (5-13)	9 (5-13)	6 (3-10)	9 (5-12)	13 (8-18)
Respiratory support received					
No oxygen received	501 (24%)	1034 (24%)	1535 (100%)	0 (0%)	0 (0%)
Oxygen only	1279 (61%)	2604 (60%)	0 (0%)	3883 (100%)	0 (0%)
Invasive mechanical ventilation	324 (15%)	683 (16%)	0 (0%)	0 (0%)	1007 (100%)
Previous diseases					
Diabetes	521 (25%)	1025 (24%)	342 (22%)	950 (24%)	254 (25%)
Heart disease	586 (28%)	1171 (27%)	519 (34%)	1074 (28%)	164 (16%)
Chronic lung disease	415 (20%)	931 (22%)	351 (23%)	883 (23%)	112 (11%)
Tuberculosis	6 (<0.5%)	19 (<0.5%)	8 (1%)	11 (<0.5%)	6 (1%)
HIV	12 (1%)	20 (<0.5%)	5 (<0.5%)	21 (1%)	6 (1%)
Severe liver disease	37 (2%)	82 (2%)	32 (2%)	72 (2%)	15 (1%)
Severe kidney impairment	167 (8%)	358 (8%)	120 (8%)	253 (7%)	152 (15%)
Any of the above	1174 (56%)	2417 (56%)	911 (59%)	2175 (56%)	505 (50%)
SARS-Cov-2 test result					
Positive	1702 (81%)	3553 (82%)	1198 (78%)	3144 (81%)	913 (91%)
Negative	213 (10%)	397 (9%)	182 (12%)	398 (10%)	30 (3%)
Test result not yet known†	189 (9%)	371 (9%)	155 (10%)	341 (9%)	64 (6%)

11’320 patients randomized between 19.03.-08.06.20

Mean age was 1.1 year higher in those allocated to dexamethasone:

- RR adjusted for baseline age

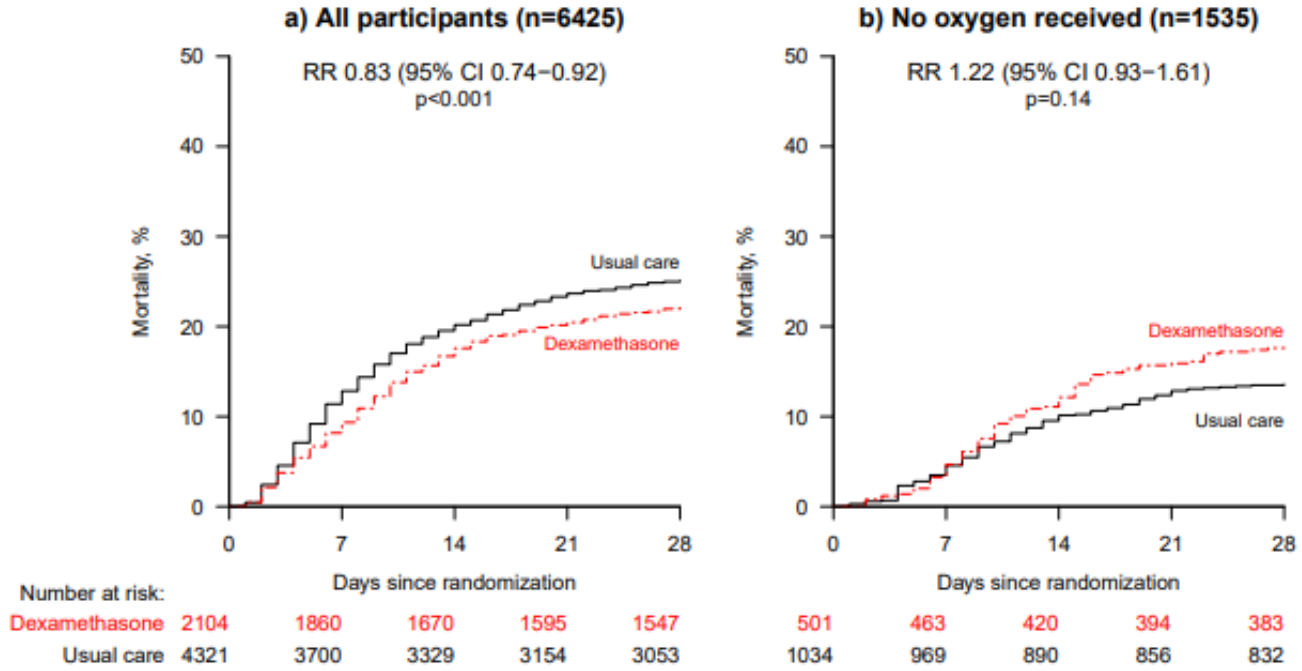
> 50% of patients with at least one major comorbidity

82% had laboratory confirmed cases

Table 2: Effect of allocation to dexamethasone on main study outcomes

	Treatment allocation			
	Dexamethasone (n=2104)	Usual care (n=4321)	RR (95% CI)	p-value
Primary outcome:				
28-day mortality	454 (21.6%)	1065 (24.6%)	0.83 (0.74-0.92)	<0.001

Figure 1: 28−day mortality in all patients (panel a) and separately according to level of respiratory support received at randomization (panels b−d)



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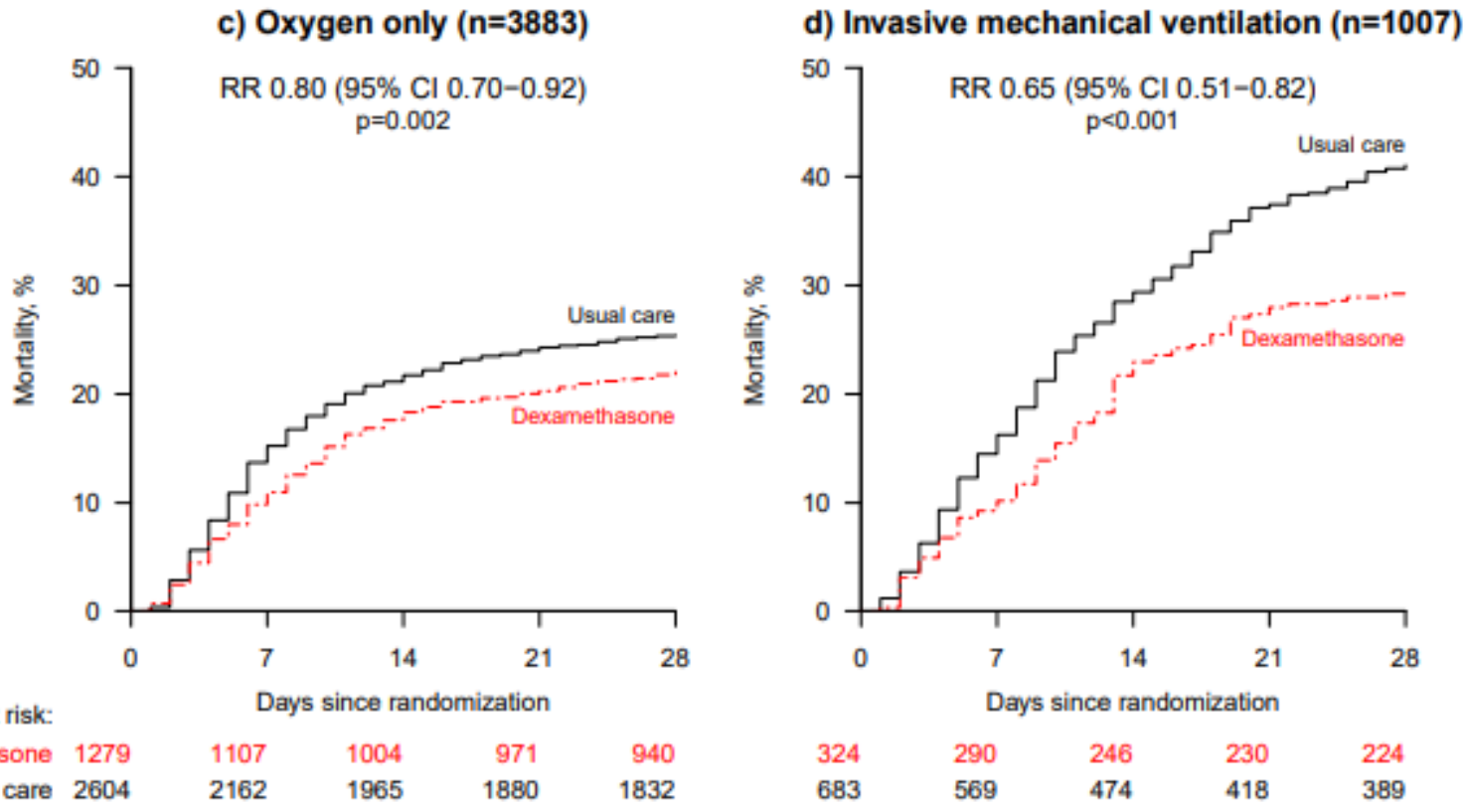

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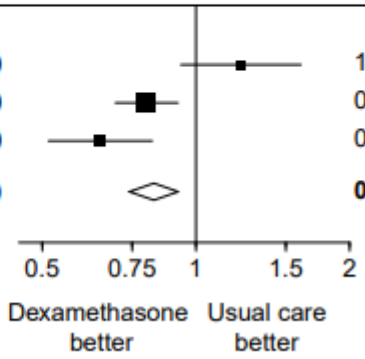
Figure 2: Effect of allocation to dexamethasone on 28−day mortality by level of respiratory support received at randomization

Respiratory support at randomization	Dexamethasone	Usual care	RR (95% CI)
No oxygen received	85/501 (17.0%)	137/1034 (13.2%)	1.22 (0.93−1.61)
Oxygen only	275/1279 (21.5%)	650/2604 (25.0%)	0.80 (0.70−0.92)
Invasive mechanical ventilation	94/324 (29.0%)	278/683 (40.7%)	0.65 (0.51−0.82)
All participants	**454/2104 (21.6%)**	**1065/4321 (24.6%)**	**0.83 (0.74−0.92) p<0.001**

Trend across three categories: χ^2_1=11.49; p<0.001



- 28-day mortality in the usual care group highest in those who were receiving ivm, lowest among those with no oxygen
- Greatest absolute reduction in 28-day mortality seen among patients on ivm
- 1 death prevented by treatment of 8 patients requiring ivm, resepctively 1 by 25 requiring oxygen

Table 2: Effect of allocation to dexamethasone on main study outcomes

	Treatment allocation			
	Dexamethasone (n=2104)	Usual care (n=4321)	RR (95% CI)	p-value
Primary outcome:				
28-day mortality	454 (21.6%)	1065 (24.6%)	0.83 (0.74-0.92)	<0.001
Secondary outcomes:				
Discharged from hospital within 28 days	1360 (64.6%)	2639 (61.1%)	1.11 (1.04-1.19)	0.002
Receipt of invasive mechanical ventilation or death*	425/1780 (23.9%)	939/3638 (25.8%)	0.91 (0.82-1.00)	0.049
Invasive mechanical ventilation	92/1780 (5.2%)	258/3638 (7.1%)	0.76 (0.61-0.96)	0.021
Death	360/1780 (20.2%)	787/3638 (21.6%)	0.91 (0.82-1.01)	0.07

RR=Rate Ratio for the outcomes of 28-day mortality and hospital discharge, and risk ratio for the outcome of receipt of invasive mechanical ventilation or death (and its subcomponents). Estimates of the RR and its 95% confidence interval are adjusted for age in three categories (<70 years , 70-79 years, and 80 years or older). * Analyses exclude those on invasive mechanical ventilation at randomization.

- Shorter duration of hospitalization: median 12 vs 13 days
- Greater probability of discharge within 28 days

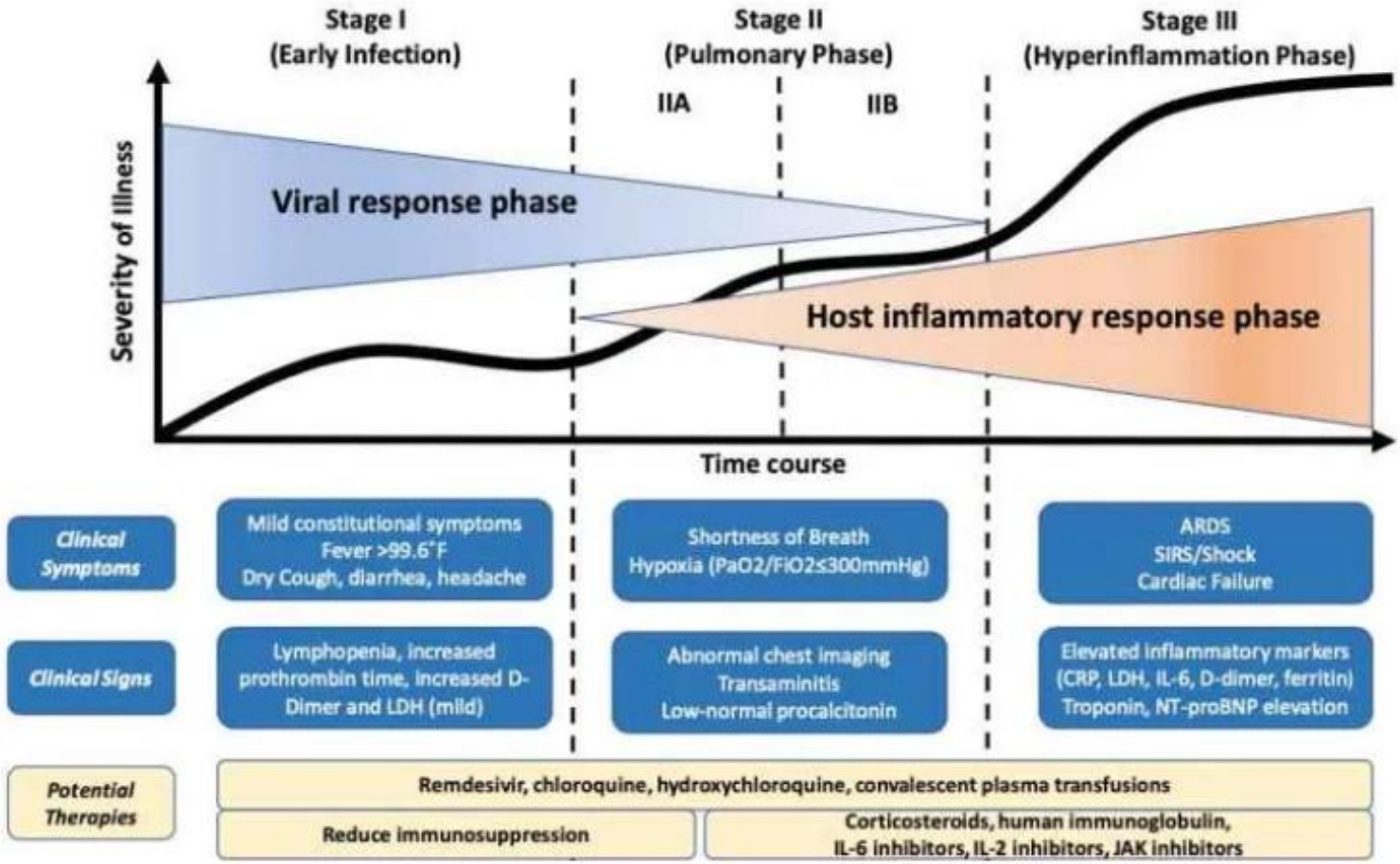
- Patients progressing to ivm was lower in those allocated to dexamethasone (RR 0.91), with greater effect in those receiving oxygen at randomization

Limitations

- Lack of physiological data fo patients (laboratory values, viral load)
- Open label (risk for systemic bias)
- Unknown final outcome (not died and still at hospital at 28d)

Diskussion

- Beneficial effect of corticosteroids dependent on the right dose, the right time and the right patient
- Greater mortality benefit in patients who require respiratory support and those after the first week of illness
- Using Dexamtheasone to early is potentially harmful



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Vielen Dank für die Aufmerksamkeit

To good to be true?