First results COVADIS project 2020-04-24

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Project summary

The COVADIS project
Covid-19 appears to be a very homogeneous disease. It mainly affects people> 50 years old, male with cardiovascular comorbidities. It is characterized by severe hypoxemia, radiological ground glass opacities, worsening during the first 7-10 days. If many unknowns still persist, this great homogeneity of presentation was previously unknown in acute pathologies treated in intensive care unit.
Despite expert recommendations, tretament for Covid-19 is not based on high levels of evidence. The treatments applied vary from one country to another, from one center to another and even from one patient to another.
We can define 3 main axes in the treatment of patients:

1. Antiviral treatment: effective in vitro candidates mainly Remdesivir, Lopinavir / ritonavir, Hydroxychloroquine,

2. Immunomodulation: corticotherapy from the start as recently suggested for acute respiratory distress syndromes (ARDS) not Covid19 or delayed to D7-D10 (Chinese recommendations) but the WHO recommends against it, other leads are being studied : inhibition of IL-6 in particular,

3. Ventilatory support: the level of PEEP to apply is uncertain (high compliance) the benefit of the paralysis as well as the risk of ventilation in pressure support (PSILI) is unknown.

In application with the ethical rules, each ICU tries to provide the best care to the patients, but the lack of solid scientific data and the convictions of each, lead to significant disparities in care.

The main objective of the study was to establish an observational register of patients suffering from moderate to severe ARDS Covid-19 by collecting the strategies used in order to be able to detect a possible signal of high efficacy or of deleterious effect and to transmit these results to the medical community as quickly as possible.

We hypothesize that, given the great homogeneity of the patients, the biases will be

limited and fairly easily adjusted, making it possible to consider differences in practice between the centers as pseudo-randomization.

In order to meet the objectives of rapid results, the number of variables collected was extremely limited.

Participating centers consecutively included patients with the criteria below

- Patients over the age of 18,
- moderate to severe ARDS according to the Berlin definition (patients with PaO2 / FiO2 <200 mmHg and PEEP + 5 cmH2O in invasive ventilation)
- PCR SARS-CoV2 positive,

were excluded patients

- having had cardiac arrest before admission to intensive care,
- having required support by ECMO within the first 24 hours,
- suffering from COPD of stage Gold 3 or 4, chronic respiratory insufficiency with oxygen at home

The main early judgment criteria is the ventilatory mode on D14:
Controlled volume or ECMO, pressure support tolerated for 24 hours, Extubation, death

The main late judgment criteria is the VFD at D28

The Secondary Assessment Criteria are:
On D14: death, extubated patient, use of ECMO, measured compliance, secondary infection of the lungs, renal impairment (maximum serum creatinine, extra-renal purification)

At D28: proportion of patients extubated, proportion of deaths, cardiac dysfunction requiring inotropic administration, pulmonary embolism, DVT.

The analyzes are performed every 50 patients in a group. The comparison of the ventilatory mode is made by Chi-2, those of the VFD by Mann-Whitney, as soon as the numbers are sufficient, multivariate analyzes will be carried out.
The other judgment criteria will be given without statistical test taking into account repeated comparisons

Results. 1st Analysis 1 - 24 April 2020. 282 patients included from 17 centres
Anti-viral treatment

	Non N= 53	Lopi/Rito N=45	HCQ N=144	Remde N=6	Bitherapy$ N= 34	p
Age mean (DS)	63,7 (11)	64,5 (11)	64 (10)		61 (11)	Nd
Sex Man N (%)	40 (76)	37(82)	110 (76)		30 (88)	Nd
BMI	30 (5)	28 (4)	29,9 (5)		29,4 (4)	Nd
Hypertension	36 (68)	20 (44)	83 (58)		20 (59)	Nd
Chronic respiratory disease	8 (15)	13 (29)	20 (14)		3 (9)	Nd
Charlson score	1 (0-3)	1 (0-2)	1 (0-2)		0 (0-2)	Nd
Vt (mL)	409 (44)	407 (50)	427 (70)		418 (34)	Nd
Vt in IBW ml/kg	6,3 (0,8)	6,1 (0,6)	6,5 (1)		6,1 (0,6)	Nd
Peep (cmH2O)	10 (3)	11 (3)	12 (3)		12 (3)	Nd
Plateau (cm H2O) N=38/33/134/29	23 (4)	22 (4)	24 (4)		23 (4)	Nd
Compliance N=38/33/134/29	37 (19)	47 (27)	37 (12)		40 (10)	Nd
P/F	136 (47)	161 (62)	131 (61)		122 (47)	Nd
FiO2	80 (60-100)	70 (60-90)	85 (60-100)		70 (50-100)	Nd
Paralysis	50 (94)	38 (84)	125 (87)		31 (91)	Nd
Length of paralysis + N= 51/44/141/33	2 (2-6)	4 (1-9)	5 (2-10)		6 (3-12)	Nd
NO	3 (6)	3 (7)	27 (19)		3 (9)	Nd
Prone position	40 (76)	28 (62)	132 (92)		27 (79)	Nd
Delay symptoms-treatment	ND	8 (6-10)	8 (5-10)		8 (6-10)	Nd
Macrolides	23 (43)	39 (87)	113 (79)		15 (44)	Nd
Azythromycine among macrolide	2 (9)	6 (15)	81 (72)		5 (33)	Nd
Corticosteroids N= 44/43/144/34*	7 (16)	7 (16)	42 (29)		8 (24)	Nd
Immunomodulation	1	0	6		0	Nd
Co-infection	1 (2)	1 (2)	24 (17)		6 (18)	Nd
Superinfection (à J14)	26 (50)	22 (50)	70 (50)		22 (65)	Nd
ECMO	5 (9)	1 (2)	13 (9)		9 (27)	Nd
Ventilatory mode D14$ **Death** **VC-ECMO-other** **Pressure Support** **Extubated**	 **12 (23)** **14 (26)** **11 (21)** **16 (30)**	 **8 (18)** **17 (38)** **9 (20)** **11 (24)**	 **36 (25)** **47 (33)** **33 (23)** **27 (19)**		 **7 (21)** **14 (42)** **7 (21)** **5 (15)**	 **0,74**
D14 Compliance (if VC) N= 9/15/41/12	29 (14)	38 (23)	30 (13)		29 (10)	Nd
Alive at D14	41 (77)	37 (82)	108 (75)		27 (79)	Nd
Renal Failure No N =244 Yes wo RRT RRT	21 (48) 19 (43) 4 (9)	15 (38) 11 (28) 14 (35)	68 (53) 39 (31) 21 (16)		12 (38) 16 (50) 4 (12,5)	Nd
Max Creat n=40/30/112/32	110 (83-201)	195 (89-461)	117 (83-276)		152 (94-388)	Nd
Cardiac involvement n= 227	3 (7)	5 (15)	21 (18)		2 (7)	Nd
max Troponine (xN)						Nd

Inotropes O/N						Nd
PE n= 43/33/122/30	6 (14)	4 (12)	22 (18)		7 (23)	Nd
DVT n= 40/33/125/29	4 (10)	3 (9)	10 (8)		2 (7)	Nd
Alive at D28 n= 32/32/95/29	16 (50)	16 (50)	46 (48)		18 (62)	Nd
D28 VFD N= 32/27/80/25	***2,5 (0-18)***	**0 (0-16)**	**0 (0-13)**		**4 (0-14)**	**0,42**

HCQ= hydroxychloroquine, RRT = Renal replacemnt therapy
$ 28 HCQ + L/R et 6 HCQ + Remdesivir. Possible center effect.
* Some patients were randomized in a blind RCT steroids vs placebo and are considered as missing data
+ Patients without paralysis were coded with 0 days
$ 2 missing data but with D14 alive status recorded

Associated factors with AKI within 14 days after intubation N = 248

	AKI + N= 131	AKI – N=117	p
Age	66 (9)	61 (11)	Nd
Sex Man N (%)	106 (81)	85 (72)	Nd
BMI	30 (5)	29 (5)	Nd
Hypertension	91 (70)	54 (47)	Nd
Uncomp DM	28 (21)	21 (18)	Nd
Comp DM	17 (13)	5 (4)	Nd
CKD	18 (14)	4 (3)	Nd
PAD	16 (12)	4 (3)	Nd
MI	16 (12)	9 (8)	Nd
Stroke	7 (5)	4 (3)	Nd
Charlson	2 (0-3)	1 (0-1)	Nd
Peep (cmH2O)	11,6 (3)	11,1 (3)	Nd
Plateau (cm H2O)	23,6 (4)	23,8 (4)	Nd
P/F	133 (58)	138 (62)	Nd
FiO2	80 (60-100)	80 (60-100)	Nd
Paralysis	111 (85)	106 (91)	Nd
ECMO	13 (10)	14 (12)	Nd
NO	13 (10)	18 (15)	Nd
Hydroxychloroquine	80 (61)	80 (68)	Nd
Lopinavir/ritonavir	41 (31)	23 (20)	Nd
Remdesivir	7 (5)	5 (4)	Nd
Corticosteroids* n=127/114	33 (26)	24 (21)	Nd
Macrolides	88 (67)	78 (67)	Nd
Co-infection	19 (15)	13 (11)	Nd
Superinfection (à J14)	72 (56)	53 (46)	Nd
D14 ventilatory mode **Death** **VC-ECMO-other** **Pressure support** **Extubated**	 48 (37) 42 (33) 21 (16) 18 (14)	 16 (14) 39 (33) 24 (21) 38 (33)	 **< 0,001**
Alive at D14	83 (63)	101 (86)	Nd
Max Creat D28 n= 119/98	241 (145-484)	84 (64-98)	Nd
Cardiac involvment N= 51/47	25 (20)	5 (5)	Nd
Troponine max (xN)			
Inotrope n= 25/5	16 (64)	4 (80)	Nd
PE n= 121/111	17 (14)	20 (18)	Nd
Alive at D28 n=99/88	35 (34)	62 (70)	Nd
D28 VFD n= 87/81	0 (0-0)	12 (0-18)	**< 0,001**

DM : diabetes Mellitus, comp = complicated, PAD : peripheric arterial disease, MI myocardial infarction

*some patients were included in a RCT steroids vs placebo

Discussion

The authors don't discuss their results regarding existing scientific data given the evolving litterature.

They underline the limitations of these results :
- the patients were not randomised and were treated in different units
- hence, other factors may induce confusion bias
- some patients may have been treated with a type of treatment because of worsening of their status, creating an indication bias
- adverse events were not systematically collected
- some follow up data are missing (indicated in the table)
- data were not monitored, reporting bias can not be excluded
- given that analyes will be repeated across time, the number of statistical test have been limited to the 2 predefined primary endpoint. Physicians have to judge the clinical relevance of some observed differences.

These data have not been peer reviewed

This list is not exhaustive

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