Convalescent plasma therapy with high titers of neutralizing antibodies to reduce mortality in patients with COVID-19 associated ARDS: the Belgian randomized CONFIDENT trial.

Misset B (1), Piagnerelli M (2), Hoste E (3), Dardenne N (4), Grimaldi D (5), Michaux I (6), Dumoulin A (7), Jorens P (8), van der Hauwaert E (9), De Waele E (10), Vallot F (11), Lamote S (12), Swinnen W (13), Fraipont V (14), de Mey N (15), De Schryver N (16), de Wit S (17), Layios N (1), Mesland JB (18), Meyfroidt G (19), Moutschen M (1), Compernolle V (20), Gothot A (1), Desmecht D (4), Taveira da Silva Pereira MI (1) Garigliany M (4), Najdovski T (20), Bertrand A (1), Donneau AF (4), Laterre PF (18)

(1) University Hospital, Liège; (2) Marie-Curie Hospital, Charleroi; (3) University Hospital, Gent; (4) Liège University; (5) Erasme University Hospital, Brussels; (6) Godinne University Hospital, Namur; (7) Delta General Hospital, Roeselare; (8) University Hospital, Antwerpen; (9) Imelda General Hospital, Bonheiden; (10) University Hospital, Jette, Belgium; (11) Wallonie Picarde General Hospital, Tournai; (12) Groeninge General Hospital, Kortrik; (13) Sint Blasius General Hospital, Dendermonde; (14) Citadelle General Hospital, Liege; (15) OLV General Hospital, Aalst; (16) Saint-Pierre Medical Clinic, Ottignies; (17) Saint-Pierre University Hospital, Brussels; (18) Saint-Luc University Hospital, Brussels; (19) University Hospital, Leuven; (20) Blood Services from the Red Cross, Mechelen and Suarlé.

Introduction

Passive immunization with plasma collected from convalescent patients has been used to treat COVID-19. Therapy with plasma collected from convalescent patients has been proposed to provide passive immunization to the patients at risk of developing severe COVD-19. Data from the first 20,000 patients transfused with COVID-19 convalescent plasma in USA showed that convalescent plasma is safe and carries a very low risk of complication (Joyner 2020).

Few trials used plasma with documented high titers of neutralizing antibodies (Devos 2021).

Most trials showed a positive effect in non hospitalized patients (Sullivan 2022) or in early disease. ARDS at baseline was excluded from most studies (Simonovitch 2020) targeting severe disease. One large trial targeting a critically ill population included MV patients (REMAP-CAP 2021). It used plasma that had been tested for total antibodies against SARS-CoV-2 but not neutralizing capacity. In this trial, MV at baseline was used in 30 % of the patients and favored plasma use in a pre-specified post-hoc subgroup analysis.

Hypothesis

Passive immunization with plasma collected from convalescents and high titers of neutralizing antibodies may reduce mortality in patients with COVID-19 associated ARDS when administered early after the introduction of MV.

Methods

Organization

Plasmas were collected and delivered by the Belgian Red Cross. The steering committee involved intensivists, infectious diseases, Red Cross, blood bank, statisticians and a patients' representative. The data safety and monitoring board involved Jean Chastre (Intensive care, Paris), Tom van der Poll (Infectious diseases, Amsterdam), Jérôme Pugin (Intensive care, Geneva), Olivier Lesieur (Intensive care, La Rochelle), Murielle Mauer (Statistics, EORTC, Brussels).
Funded by a grant from KCE # COV201004.

Inclusion criteria

Adult, Clinical Frailty Scale < 6, SARS-CoV-2 pneumonia (CT scan < 10 days, PCR < 15 days), MV <5 days, inform consent from patient or proxy.

Exclusion criteria

Pregnancy, prior episode of transfusion-related side effect, medical decision to limit therapy, participation in another trial on therapy for COVID-19.

Design

Stratification: (1) MV <= 48h, and (2) MV > 48h and <= 5 days (120 h)
Randomization to allocate the study intervention:
(1) 2 x 250 mL bags of **convalescent plasma with 1/320° neutralizing Ab** against COVID-19,
(2) Standard of care.

Endpoints

Primary : **mortality at day 28**
Secondary :
duration of MV, number of organ failures, viral load, inflammation (CRP, IL-6), mortality at day 90, functional and psychological status at day 90
Adverse events

Sample size calculation

Expected mortality in the standard of care group : 40 %, and in the convalescent plasma group : 30 %, alpha risk = 0,05, beta risk = 0,20. N = 250 x 2 = **500 patients to include**

Interim analyses for safety and / or futility at 100, 200, 300, 400. Only the DSMB had access to the results of the interim analyses.

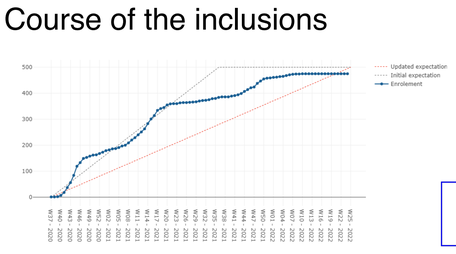
Conclusion

The administration of plasma collected from convalescent donors and documented with high titers of neutralizing antibodies to patients with COVID-19 associated ARDS within 5 days of mechanical ventilation significantly reduced mortality at day 28.
In the pre-specified analysis, this was driven by the patient group included within 48 hours.

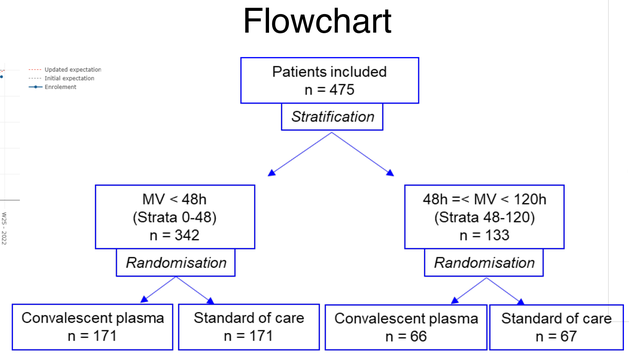
Results

17 centers in Belgium. 475 patients included between October 2020 and March 2002. Decision to stop on March 9, 2022 due to lack of recruitment, likely due to reduced virulence of Omicron variant.

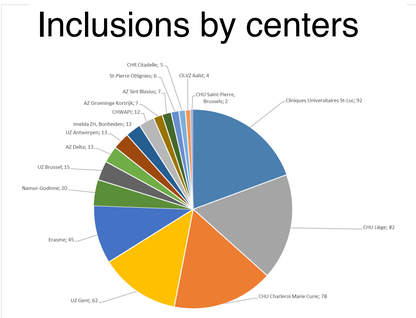
Course of the inclusions



Flowchart



Inclusions by centers



Patients at inclusion

	Convalescent Plasma	Standard of care	*p*
	N = 237	N = 238	
Age, years	64 [55-71]	64 [56-70]	*0.96*
BMI, kg/m²	30.5 [26.5-34.9]	29.7 [26.5-34.3]	*0.53*
PaO2/FiO2, mmHg	117 [90-162]	128 [93-160]	*0.30*
APACHE 2 score, points	**13.0 [9.0-18.0]**	**13.0 [9.0-17.0]**	***0.82***
SOFA, points	6.0 [4.0-8.0]	6.0 [4.0-8.0]	*0.39*
CRP, mg/L	**126 [67-191]**	**110 [55-188]**	***0.20***
Diabetes, yes	34.2 %	38.7 %	*0.31*
COPD, yes	11.4 %	10.1 %	*0.67*
Chronic renal failure	13.5 %	12.6 %	*0.79*
Time from hospital admission, days	**4.6 [2.6-6.7]**	**5.4 [2.8-7.7]**	***0.11***

Severity of ARDS at inclusion (Berlin criteria)

Category of ARDS at baseline	Convalescent Plasma	Standard of care
	N = 237	N = 238
	N (%)	N (%)
Mild (P/F = 200-300 mmHg)	24 (10.4)	21 (9.1)
Moderate (P/F = 100-200 mmHg)	126 (54.5)	142 (61.2)
Severe (P/F < 100 mmHg)	81 (35.1)	69 (29.7)

Concomitant medication against COVID-19

	Convalescent Plasma	Standard of care	*p*
	N = 237	N = 238	
	N (%)	N (%)	
Hydroxychloroquine	1 (0.4)	0 (0.0)	*1.00*
Azythromycin	10 (4.2)	4 (1.7)	*0.10*
Remdesivir	13 (5.5)	14 (5.9)	*0.84*
Anti-IL-6R	12 (5.1)	7 (2.9)	*0.28*
Steroids	232 (97.9)	232 (97.5)	*0.69*
dexamethasone	*216 (91.1)*	*225 (94.5)*	
methylprednisolone	*15 (6.3)*	*8 (3.4)*	

Outcomes

Patients outcomes, by group

	Convalescent Plasma	Standard of care	*p*
	N = 237	N = 238	
	Med [IQR] or N (%)	Med [IQR] or N (%)	
Death at day 28	**84 (35.4)**	**106 (44.7)**	***0.043***
Delta CRP (D7–D0), mg/	-19 [-92 - +60]	0 [-64 - +77]	*0.08*
SOFA, day 7 in survivors	**4 [3-7]**	**5 [4-8]**	***0.01***
SOFA, day 14 in survivors	5 [3-7]	6 [4-8]	*0.06*
SOFA, day 21 in survivors	5 [3-7]	5 [3-8]	*0.28*
SOFA, day 28 in survivors	4 [3-7]	5 [3-7]	*0.92*
ECMO use	45 (19.0)	47 (19.7)	*0.85*
Vasopressor use	192 (81.0)	204 (85.7)	*0.16*
RRT use	31 (13 .1)	42 (17.6)	*0.16*
Ventilation-free days	0 [0-14]	0 [0-10]	*0.28*
Vasopressor-free days	19 [4-27]	14 [2-26]	*0.11*
RRT-free days	28 [12-28]	27 [10-28]	*0.19*

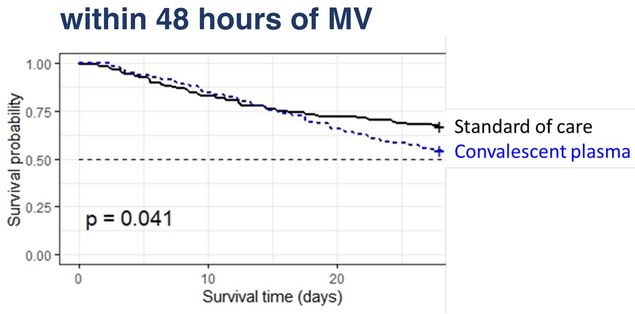
Serious adverse events

SAE, reported to sponsor	
Fatal	**184**
Refractory respiratory failure	115
Secondary infection	37
Hemorrhage	19
Metabolic	2
Cardiac failure	10
Other	1
Attributed to plasma	**0**
Non Fatal	**25**
Refractory respiratory failure	8
Secondary infection	8
Hemorrhage	4
Cardiac failure	1
Metabolic	3
Other	1
Attributed to plasma	**0**

Day-28 mortality by strata

Strata		Convalescent Plasma	Standard of care	*p*
MV <= 2 days		**n = 144**	**n = 144**	
	Death at Day-28, n (%)	**56 (32.7)**	**79 (46.2)**	***0.011***
2 days < MV < 5 days		n = 66	n = 67	
	Death at Day-28, n (%)	28 (42.4)	27 (40.3)	*0.80*

Survival curve in the strata included within 48 hours of MV



Day-28 mortality in pre-specified sub-groups

Sub-group		Convalescent Plasma	Standard of care	*p*
CRP < 118 mg/L		n = 109	n = 128	
	Death at Day-28, n (%)	37 (33.9)	55 (43.0)	*0.16*
CRP >= 118 mg/L		n = 128	n = 110	
	Death at Day-28, n (%)	47 (36.7)	51 (46.8)	*0.12*
SOFA < 6		n = 104	n = 90	
	Death at Day-28, n (%)	25 (24.0)	25 (27.8)	*0.55*
SOFA >= 6		n = 133	n = 145	
	Death at Day-28, n (%)	59 (44.4)	80 (55.2)	***0.07***
DHosp–D0 < 5 days		n = 131	n = 113	
	Death at Day-28, n (%)	41 (31.1)	45 (39.8)	*0.16*
DHosp–D0 >= 5 days		n = 103	n = 118	
	Death at Day-28, n (%)	43 (41.7)	61 (51.7)	*0.14*