Convalescent plasma for COVID19

Late, Early or Never?

For all, some or none?

Erasmus MC
Universitair Medisch Centrum Rotterdam

May 20, 2021

Antibody based therapy: How it started

Anecdotes, observational data, matched case control studies

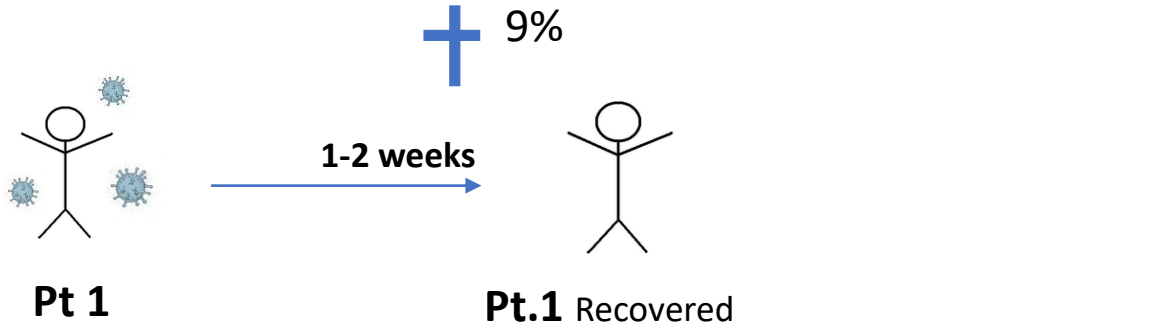
From small focused to very large simple pragmatic randomized trial

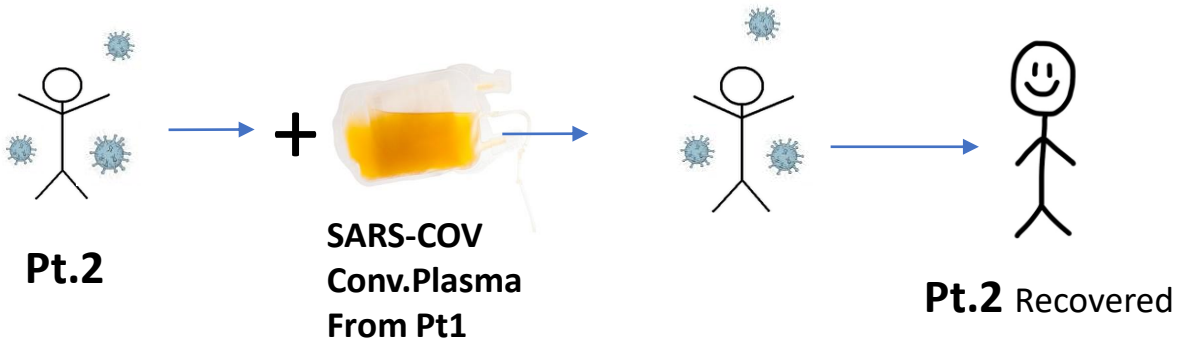
Bayesian real-time individual patient data meta-analysis

Remaining questions and results to look out for

How it started

SARS-Cov (2003) Data from 3 small studies





Plasma therapy led to :
- shorter stay (p0.001)
- lower mortality (p0.05)

Plasma given earlier in the course of disease seems to be more effective

1d after plasma infusion:
>10.000 ➡ *<10 copies*

Clin Microbiol Infect. 2004 Jul;10(7):676-8.

Eur J Clin Microbiol Infect Dis. 2005 Jan;24(1):44-6.

J Antimicrob Chemother. 2005 Nov;56(5):919-22.

Case series of convalescent plasma for COVID-19

CP transfusion date	Before CP transfusion			After CP transfusion		
	Date	Serum neutralizing antibody titers	Serum SARS-CoV-2 RNA load (Ct value)	Date	Serum neutralizing antibody titers	Serum SARS-CoV-2 RNA load (Ct value)
February 9	February 8	1:160	37.25	February 10	1:640	Negative
February 9	February 8	Unavailable	35.08	February 11	Unavailable	Negative
February 13	February 12	1:320	38.07	February 14	1:640	Negative
February 13	February 12	1:160	37.68	February 14	1:640	Negative
February 12	February 11	1:640	Negative	February 14	1:640	Negative
February 12	February 11	1:640	Negative	February 14	1:640	Negative
February 12	February 11	1:320	34.64	February 14	1:640	Negative
February 12	February 11	1:640	35.45	February 14	1:640	Negative
February 12	February 11	1:160	Negative	February 14	1:640	Negative
February 9	February 8	1:640	38.19	February 14	1:640	Negative

Table 1. Comparison of clinical features and outcomes of patients between CP treatment group and a non–CP treatment recent historic control group.

	CP treatment group (n=10)	Historic control group (n=10)	*p* value
Demographics			
Age, years	52.50 (45.00-59.50)	53.00 (46.50-60.50)	0.985
Gender			
Male	6 (60)	6 (60)	1.000
Female	4 (40)	4 (40)	
Comorbidity			
Yes	4 (40)	6 (60)	0.656
No	6 (60)	4 (40)	
Baseline laboratory parameters			
C-reactive protein	55.98 (15.57-66.67)	96.70 (33.92-173.39)	0.190
Lymphocyte	0.65 (0.53-0.90)	0.76 (0.54-1.32)	0.469
Alanine aminotransferase	42.00 (28.25-61.85)	20.35 (17.03-67.83)	0.133
Aspartate aminotransferase	38.10 (28.50-44.00)	37.35 (32.28-74.85)	0.764
Total bilirubin	12.40 (11.71-22.05)	8.70 (4.28-19.03)	0.065
SaO_2	93.00 (89.00-96.50)	93.00 (87.50-97.50)	0.923
Clinical Outcome			
Death	0(0)	3(30)	< 0.001*
Stable	0(0)	6(60)	
Improved	7(70)	1(10)	
Discharged	3(30)	0(0)	

Duan K, et al. Proc Natl Acad Sci U S A. 2020

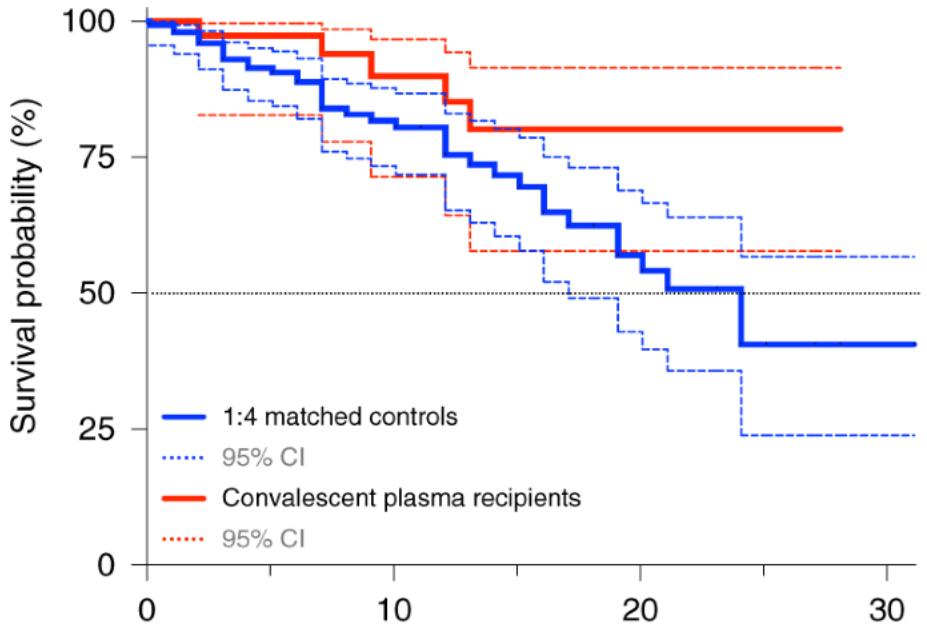
Convalescent plasma treatment of severe COVID-19: A matched control study

39 plasma recipients with severe COVID-19

159 matched controls from same time period

ConvP donors Anti-S ELISA ≥1:320

Survival improved in plasma recipients (aHR 0.34 CI 0.13–0.89)



It's a MIRACLE !

Liu STH, et al. Nat Med. 2020.

Effect of ConvP on Mortality among Hospitalized Patients with COVID-19

n=35.322 27% ventilated all received ConvP

Day 7 Mortality 8.7% in pts transfused within 3 days of diagnosis

Mortality 11.9% in pts transfused later ($p<0.001$).

Day 30 Similar findings (21.6% vs. 26.7%, $p<0.0001$)

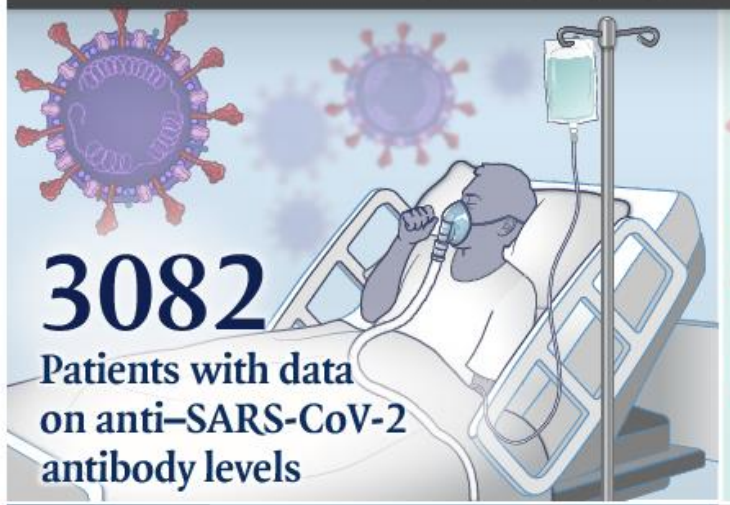
High IgG plasma : Day 7 mortality 8.9%
Medium IgG plasma : Day 7 mortality 11.6%
Low IgG plasma : Day 7 mortality 13.7% ($p=0.048$)

https://www.medrxiv.org/content/10.1101/2020.08.12.20169359v1

The NEW ENGLAND JOURNAL of MEDICINE

Convalescent Plasma Antibody Levels and Covid-19 Mortality

RETROSPECTIVE STUDY BASED ON A U.S. NATIONAL REGISTRY



3082
Patients with data on anti–SARS-CoV-2 antibody levels

	High Antibody Level	Medium Antibody Level	Low Antibody Level
	N=515	N=2006	N=561
Death within 30 days after plasma transfusion	22.3% (115 patients)	27.4% (549 patients)	29.6% (166 patients)

Relative risk (high vs. low), 0.66; 95% CI, 0.48 to 0.91

In patients not receiving mechanical ventilation, transfusion of plasma with higher antibody levels was associated with a lower risk of death.

M.J. Joyner et al. 10.1056/NEJMoa2031893

Long story short:

Biased observations led to uncontrolled use of ConvP for COVID19 in USA

Fortunately, other countries took a different approach

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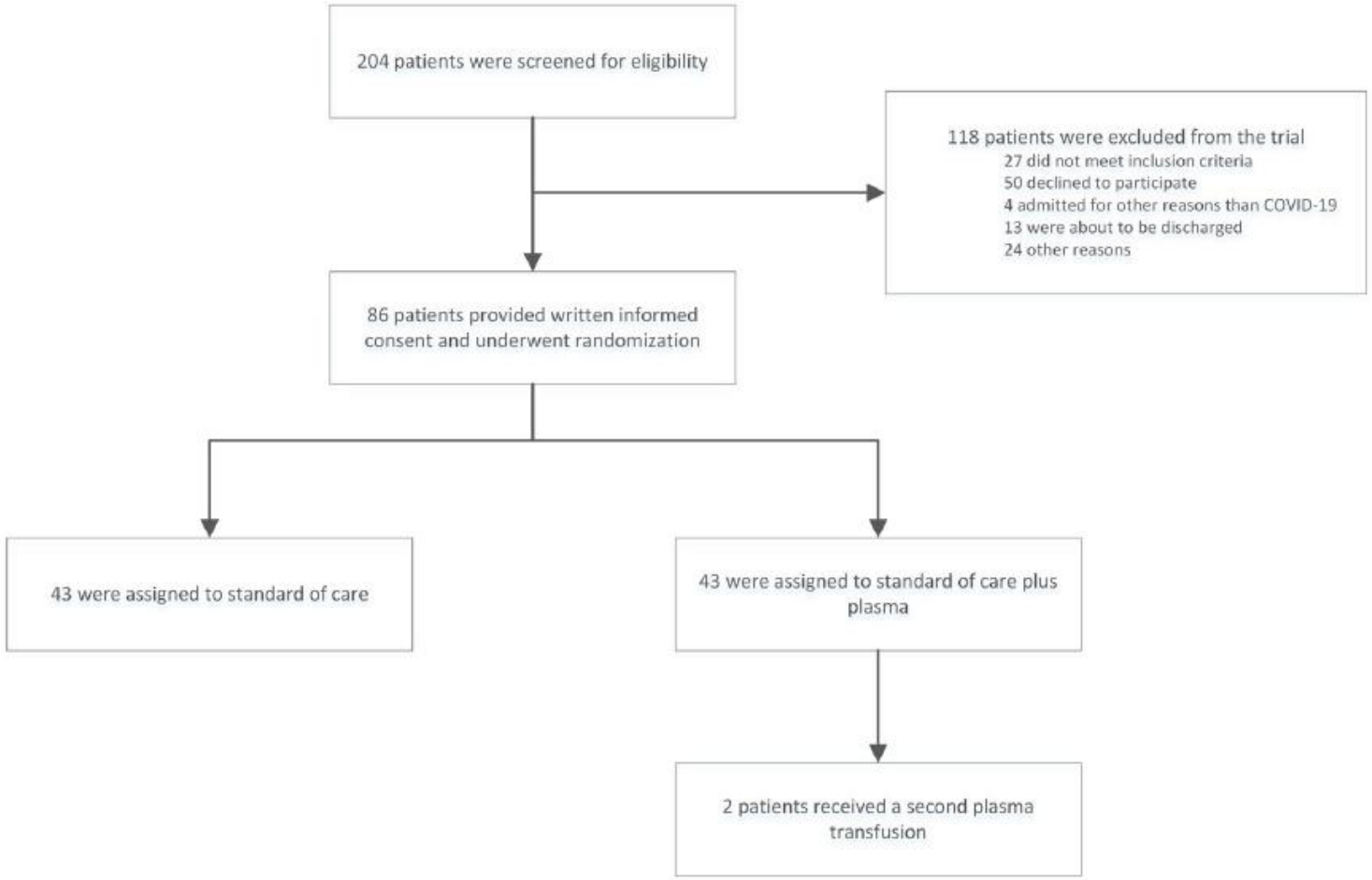
From ConCOVID to CoV-Early: The CONCOVID study



Gharbharan A et al. Medrxiv preprint and Nature Communications, 2021 in press

Questions we had at the time the ConCOVID study started

How essential is antibody based immunity against SARS-CoV-2?

What is the timing of virus neutralizing antibody formation?

Potential donors: Do all ex-patients have virus neutralizing antibodies and for how long?

Potential donors: Do all ex-patients have *enough* virus neutralizing antibodies?

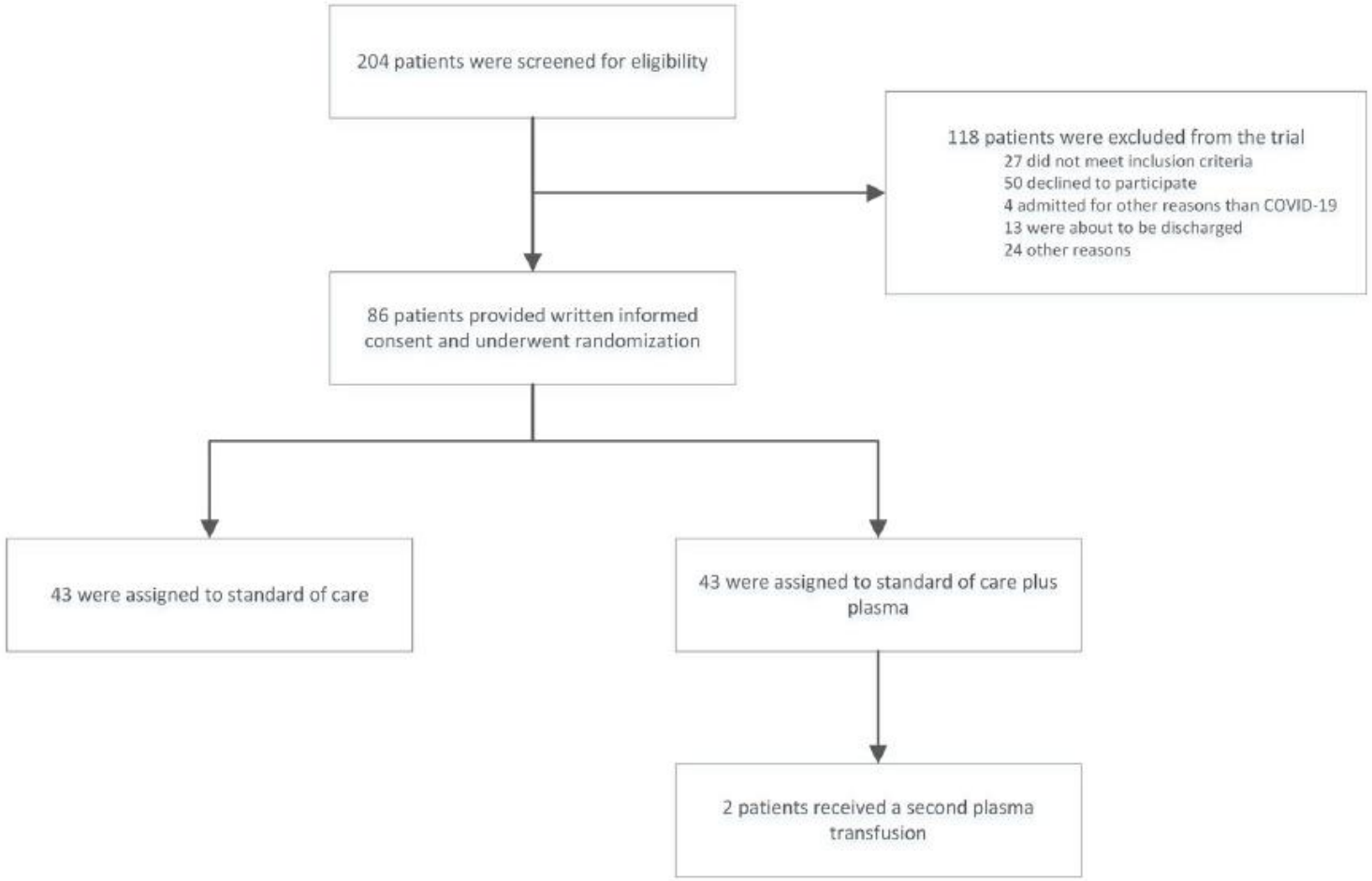
How to select the best donors efficiently? (Antibodies against S protein, RBD of S, Nucleocapsid, PRNT50, pseudovirus ...*)*

What dose is needed (given the dilution factor and consumption of administered antibodies)?

What is the best timing of antibody based therapy (window of opportunity)?

Are there risks associated with antibody based therapy (e.g. ADE)?

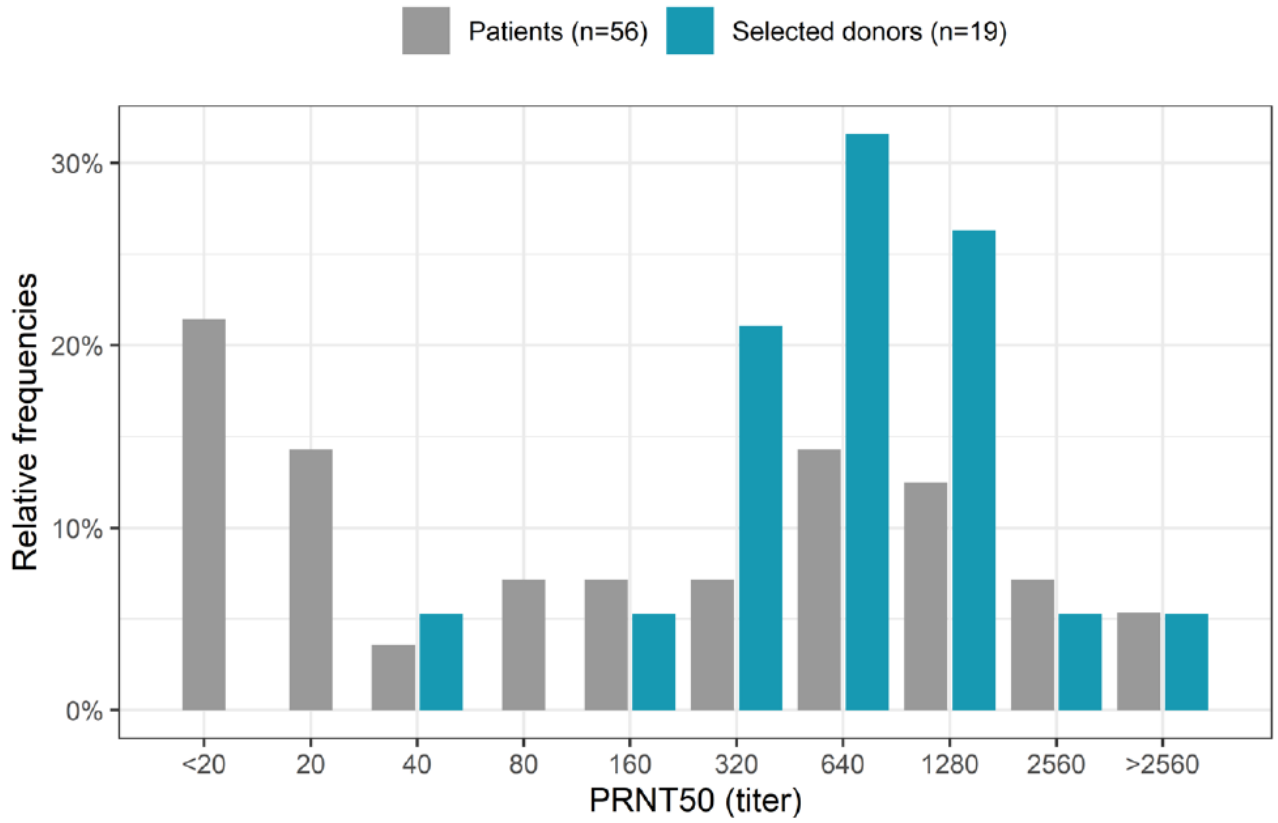
From ConCOVID to CoV-Early: The CONCOVID study

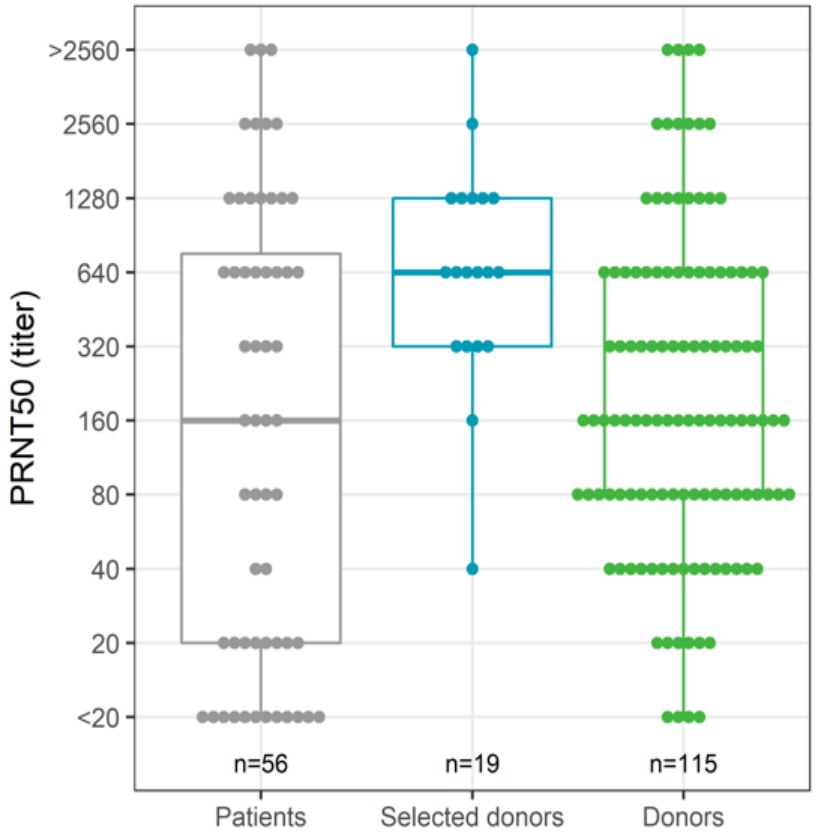


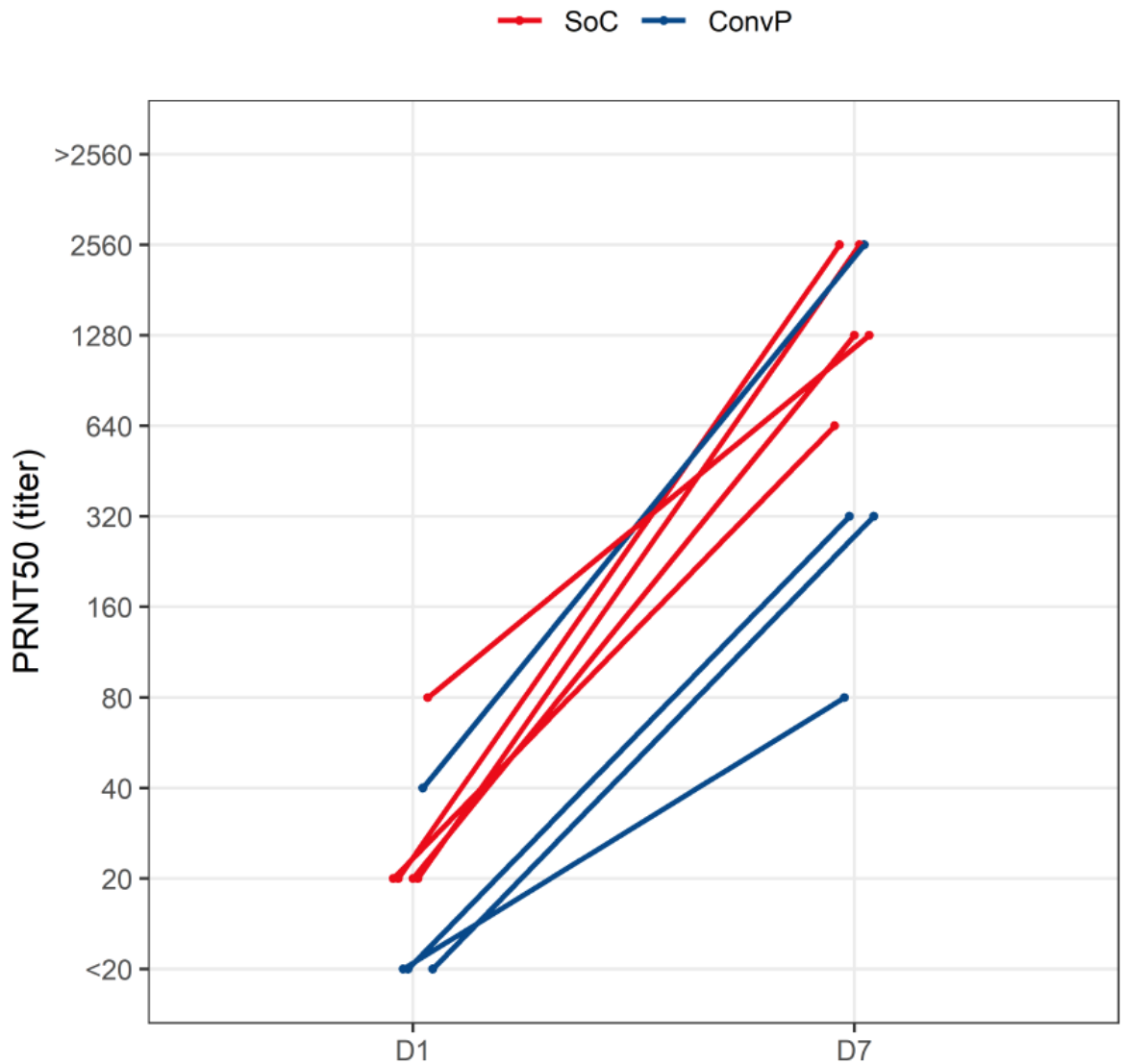
Gharbharan A et al. Medrxiv preprint and Nature Communications, 2021 in press

From ConCOVID to CoV-Early

Recruitment STOPPED June 12, 2020



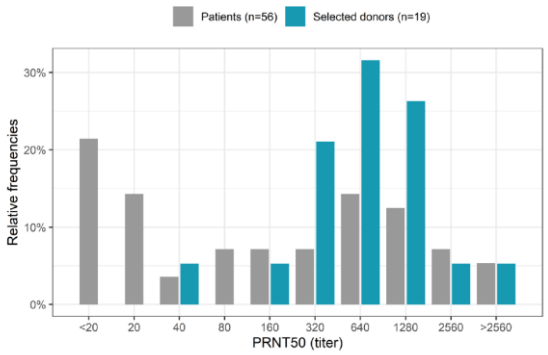



SoC
ConvP
PRNT50 (titer)
>2560
2560
1280
640
320
160
80
40
20
<20
D1
D7

ConCOVID study

Meeting with DSMB => Recruitment STOPPED June 12, 2020

The patients antibody production



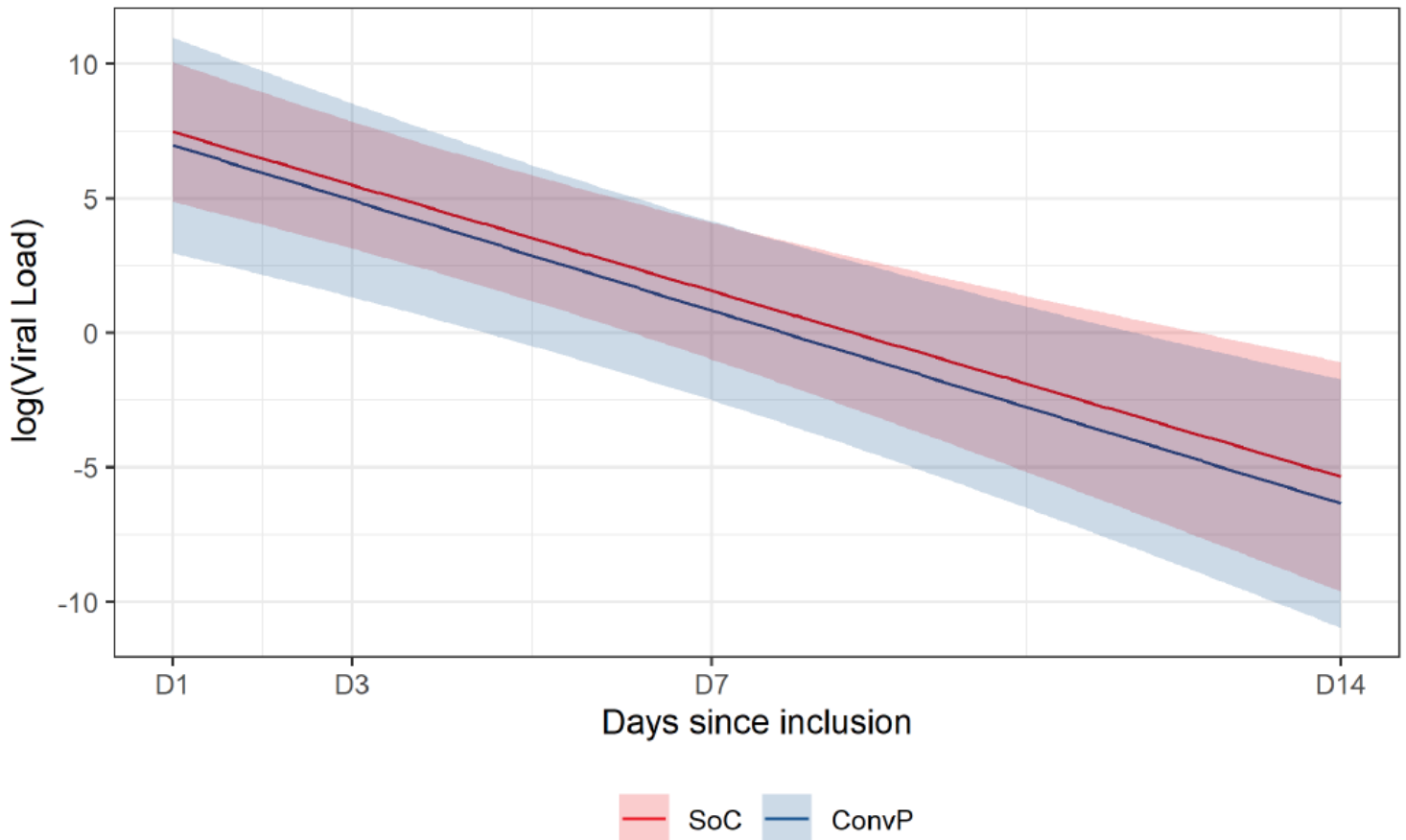
Patient's own total blood (=plasma) pool

Odds ratios and 95% CIs from unadjusted and adjusted analysis of mortality.

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	P-value
ConvP	0.472 (0.148; 1.384)	0.948 (0.195; 4.670)	0.95*
Age	-	1.097 (1.034; 1.179)	0.005
Female sex	-	0.717 (0.118; 3.932)	0.70
ICU on admission	-	6.701 (0.209; 142.602)	0.22
CRP on admission	-	1.000 (0.991; 1.009)	0.93
Lymphocyte count on admission	-	0.114 (0.013; 0.609)	0.023
FI02 on admission	-	1.022 (0.994; 1.054)	0.13
Bilirubine	-	0.873 (0.727; 0.986)	0.078

*P-value from multivariable adjusted logistic regression

Predicted evolution (solid line) and 95% CI (shaded area) of absolute log(Viral Load) in log(copies/ml) per day since enrollment (D=1) for COVID-19 patients (SoC: red, ConvP: blue) excluding subjects who had viral load equal to zero at day 1 of enrollment.



From ConCOVID to CoV-Early

PRNT50 titer was measured in 115 donors => 19 were selected
Recruitment STOPPED June 12, 2020

- Effect very unlikely in 75% with antibodies at baseline: Underpowered study
- Even in subgroup without antibodies : Antibodies appear soon after admission
- => STOP and REDESIGN

	ConVP (CP)	CP Neutr AB	Symptoms (d)	d0 Neutr AB	Prim endpoint
JAMA 6/2020 **China , n=103**	**4-13ml/kg**	**Uncertain**	**30**	**not reported**	**No difference**
Nature Comm 7/2020 **NL, n=86**	**300ml**	**High**	**10**	**75%**	**No difference**
BMJ 10/2020 **India, n=464**	**2x200ml**	**0 in 1/3 !!** **Medium**	**8**	**83%**	**No difference**
NEJM 11/2020 **Argentina, n=333**	**400-600ml**	**Medium-High**	**8**	**54%**	**No difference**

The study of a moving target: *First Corticosteroids Y/N, then B117*

ORIGINAL ARTICLE

A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia

V.A. Simonovich, L.D. Burgos Pratx, P. Scibona, M.V. Beruto, M.G. Vallone, C. Vázquez, N. Savoy, D.H. Giunta, L.G. Pérez, M..L. Sánchez, A.V. Gamarnik, D.S. Ojeda, D.M. Santoro, P.J. Camino, S. Antelo, K. Rainero, G.P. Vidiella, E.A. Miyazaki, W. Cornistein, O.A. Trabadelo, F.M. Ross, M. Spotti, G. Funtowicz, W.E. Scordo, M.H. Losso, I. Ferniot, P.E. Pardo, E. Rodriguez, P. Rucci, J. Pasquali, N.A. Fuentes, M. Esperatti, G.A. Speroni, E.C. Nannini, A. Matteaccio, H.G. Michelangelo, D. Follmann, H.C. Lane, and W.H. Belloso, for the PlasmAr Study Group*

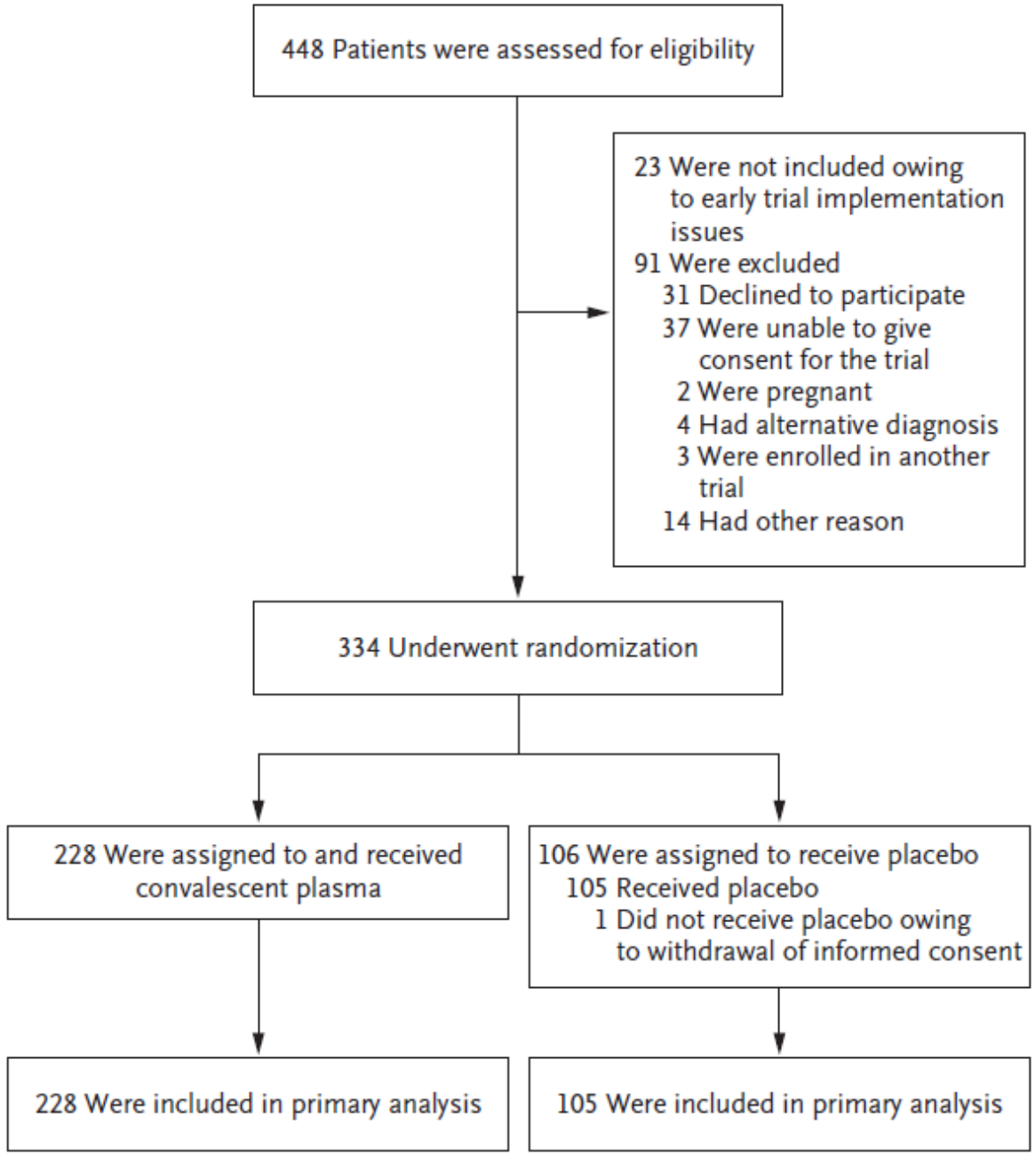
This article was published on November 24, 2020, at NEJM.org.

Admitted to hospital *and*

O2 <93% OR PaO2/FiO2 <300 OR SOFA 2

but not in ICU

1 unit of ConV Plasma
Carefully selected donors


448 Patients were assessed for eligibility
23 Were not included owing to early trial implementation issues
91 Were excluded
31 Declined to participate
37 Were unable to give consent for the trial
2 Were pregnant
4 Had alternative diagnosis
3 Were enrolled in another trial
14 Had other reason
334 Underwent randomization
228 Were assigned to and received convalescent plasma
106 Were assigned to receive placebo
105 Received placebo
1 Did not receive placebo owing to withdrawal of informed consent
228 Were included in primary analysis
105 Were included in primary analysis

A picture says more than 1000 words

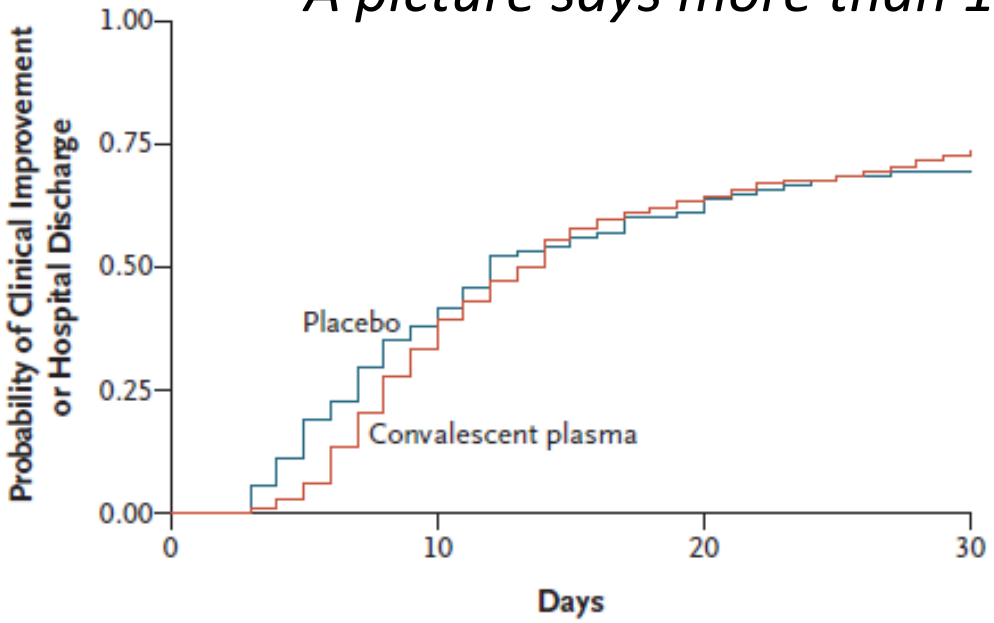


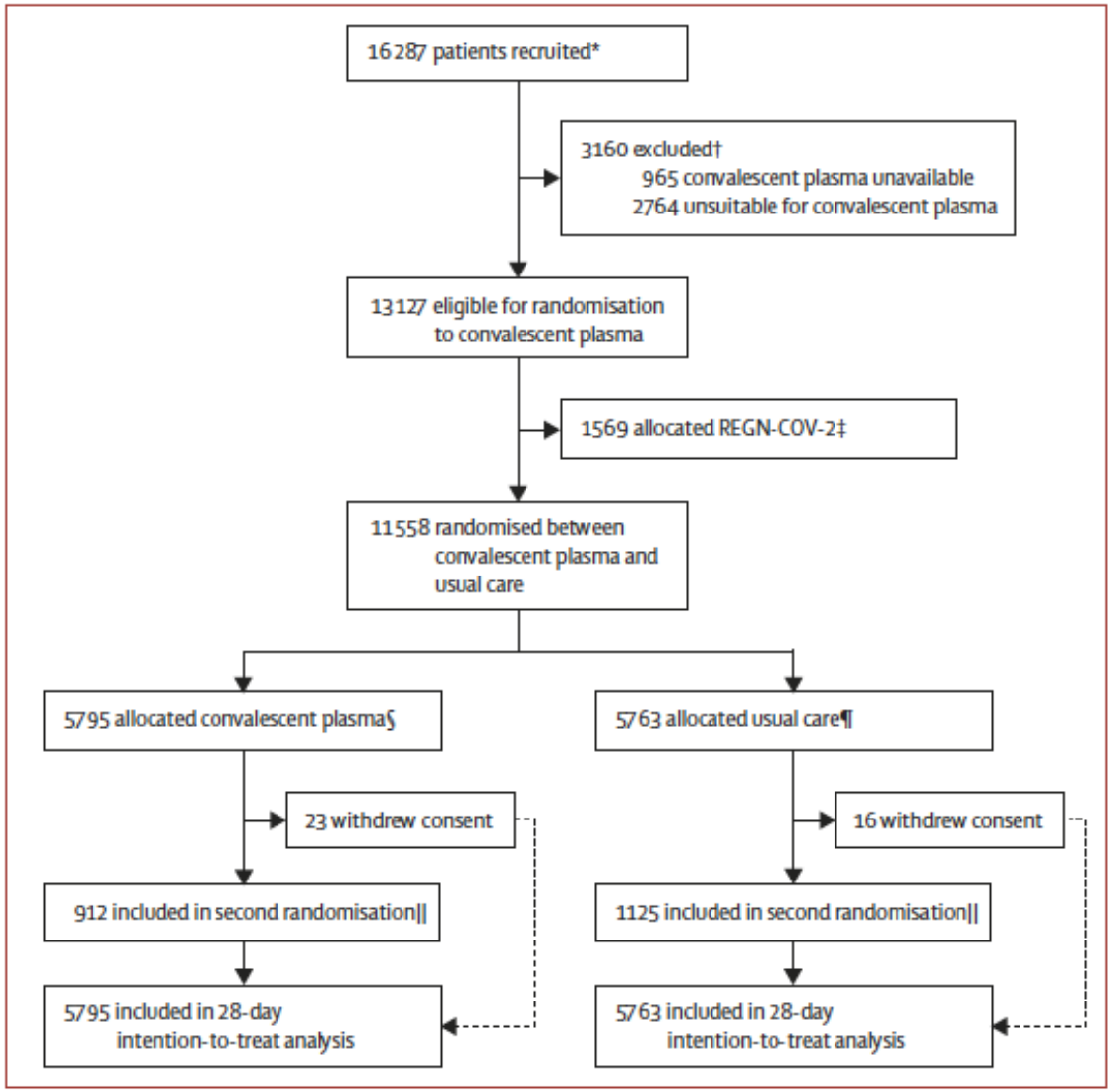
Table S3: Total SARS-CoV-2 antibodies titer in time (days) and by intervention groups.

SARS-CoV2 total antibodies titers	Baseline	day 2	day 7	day 14
Convalescent plasma group, *median (IQR)*	1:50 (0-1:800)	1:400 (1:200-1:1600)	1:3200 (1:1600-1:6400)	1:6400 (1:3200-1:12800)
Placebo group, *median (IQR)*	1:50 (0-1:1600)	1:400 (1:50-1:3200)	1:3200 (1:1600-1:6400)	1:12800 (1:3200-1:12800)
N	215	298	240	165
p value	0.955	0.044	0.806	0.449

Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial

*RECOVERY Collaborative Group**

2 units of plasma
From 2 different donors
Euroimmune ELISA antibodies >6.0

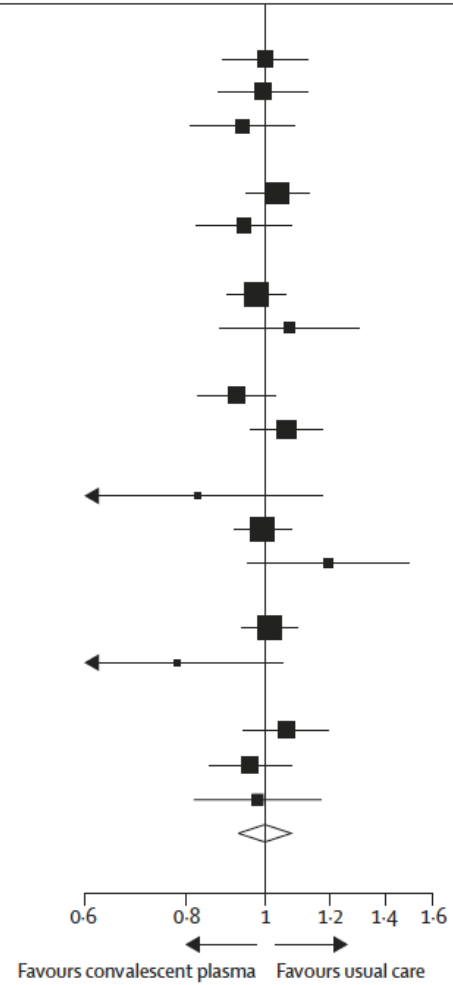


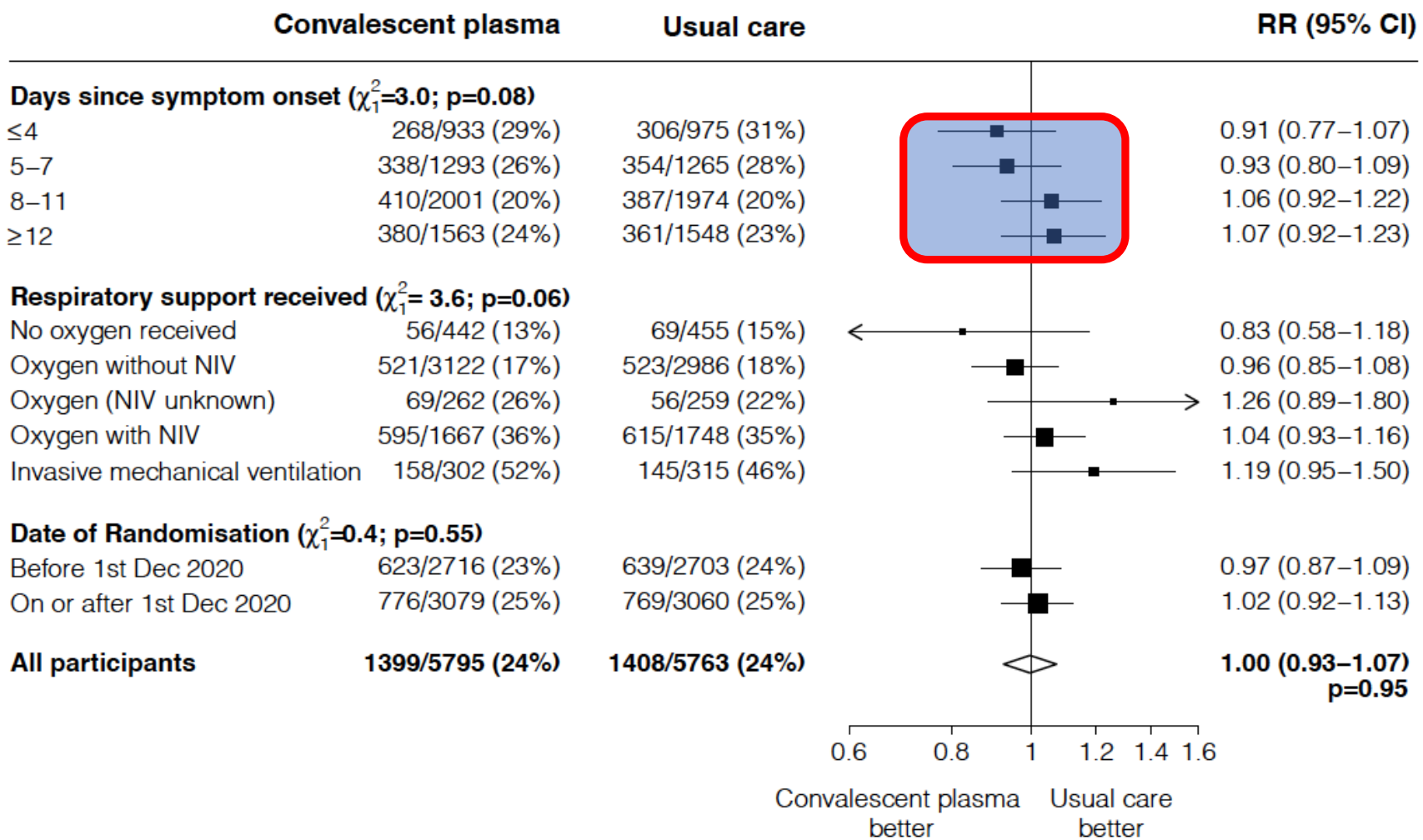
Lancet 2021 Published Online May 14, 2021

Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial

*RECOVERY Collaborative Group**

	Convalescent plasma group	Usual care group	RR (95% CI)
Age, years (χ^2_1=0·4; p=0·53)			
<70	534/3705 (14%)	545/3748 (15%)	1·00 (0·89–1·13)
70–79	495/1310 (38%)	494/1281 (39%)	0·99 (0·87–1·13)
≥80	370/780 (47%)	369/734 (50%)	0·94 (0·81–1·09)
Sex (χ^2_1=1·3; p=0·25)			
Men	953/3643 (26%)	972/3787 (26%)	1·03 (0·95–1·13)
Women	446/2152 (21%)	436/1976 (22%)	0·94 (0·82–1·07)
Ethnicity (χ^2_1=0·8; p=0·37)			
White	1111/4493 (25%)	1129/4421 (26%)	0·97 (0·90–1·06)
Black, Asian or minority ethnic	198/833 (24%)	199/887 (22%)	1·07 (0·88–1·31)
Days since symptom onset (χ^2_1=3·4; p=0·06)			
≤7	606/2226 (27%)	660/2240 (29%)	0·92 (0·82–1·03)
>7	790/3564 (22%)	748/3522 (21%)	1·06 (0·96–1·17)
Respiratory support received (χ^2_1=3·5; p=0·06)			
No oxygen received	56/442 (13%)	69/455 (15%)	0·83 (0·58–1·18)
Oxygen only	1185/5051 (23%)	1194/4993 (24%)	0·99 (0·91–1·07)
Invasive mechanical ventilation	158/302 (52%)	145/315 (46%)	1·19 (0·95–1·50)
Use of corticosteroids (χ^2_1=2·7; p=0·10)			
Yes	1314/5370 (24%)	1299/5311 (24%)	1·01 (0·94–1·09)
No	74/391 (19%)	100/413 (24%)	0·78 (0·58–1·05)
Patient SARS-CoV-2 antibody test result (χ^2_1=1·4; p=0·23)			
Positive	575/3078 (19%)	501/2810 (18%)	1·06 (0·94–1·19)
Negative	642/2016 (32%)	558/1660 (34%)	0·96 (0·85–1·07)
Not done	182/701(26%)	349/1293 (27%)	0·98 (0·82–1·17)
All participants	**1399/5795 (24%)**	**1408/5763 (24%)**	**1·00 (0·93–1·07)**
			p=0·95




Convalescent plasma
Usual care
RR (95% CI)
Days since symptom onset (χ^2_1=3.0; p=0.08)
≤4 268/933 (29%) 306/975 (31%) 0.91 (0.77–1.07)
5–7 338/1293 (26%) 354/1265 (28%) 0.93 (0.80–1.09)
8–11 410/2001 (20%) 387/1974 (20%) 1.06 (0.92–1.22)
≥12 380/1563 (24%) 361/1548 (23%) 1.07 (0.92–1.23)
Respiratory support received (χ^2_1= 3.6; p=0.06)
No oxygen received 56/442 (13%) 69/455 (15%) 0.83 (0.58–1.18)
Oxygen without NIV 521/3122 (17%) 523/2986 (18%) 0.96 (0.85–1.08)
Oxygen (NIV unknown) 69/262 (26%) 56/259 (22%) 1.26 (0.89–1.80)
Oxygen with NIV 595/1667 (36%) 615/1748 (35%) 1.04 (0.93–1.16)
Invasive mechanical ventilation 158/302 (52%) 145/315 (46%) 1.19 (0.95–1.50)
Date of Randomisation (χ^2_1=0.4; p=0.55)
Before 1st Dec 2020 623/2716 (23%) 639/2703 (24%) 0.97 (0.87–1.09)
On or after 1st Dec 2020 776/3079 (25%) 769/3060 (25%) 1.02 (0.92–1.13)
All participants 1399/5795 (24%) 1408/5763 (24%) 1.00 (0.93–1.07) p=0.95
0.6
0.8
1
1.2
1.4
1.6
Convalescent plasma better
Usual care better

QUESTION: What was the overall mortality benefit of dexamethasone in Recovery ?

RESULTS

A total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care. Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomiza-

2.8%

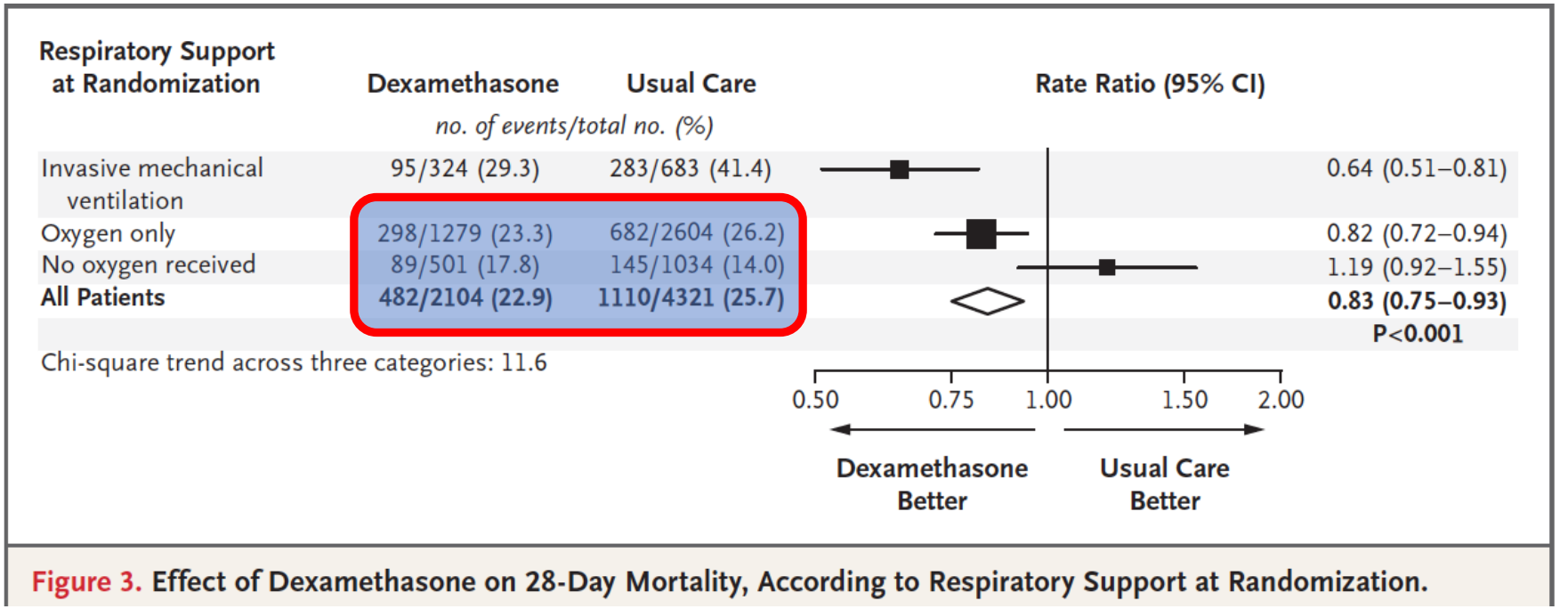


Figure 3. Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization.

Recovery:

95% not on invasive ventilation, still a 24% overall mortality ?

Subgroup analysis of 2000 patients with ≤4 days of symptoms at randomization ?

Jury still out on subgroup of antibody negative and/or <8 days of symptoms subgroups

Jury still out on dose-response as seen with observational data (MJ Joyner et al NEJM 2020)

Positive

Very large sample size, 2 units of 2 different donors

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COMPILE consortium

COntinuous **M**onitoring of **P**ooled **I**nternational Trials of Conva**LE**scent Plasma for COVID

Real-Time Individual Patient Data Bayesian Meta-Analysis of Randomized Clinical Trials

Bayesian design and stopping rules:

Proportional odds model of WHO 0-10 (11-point) scale :
Overall OR comparing the odds of a “worse” outcome with Conalescent Plasma vs Control on d14

Stopping rule: When $P \geq 0.95$ that $OR < 1.0$ and $P \geq 0.5$ that $OR < 0.8$

Interim analysis was done every 4 weeks

Thanks to Andrea Troxel, NYU Langone

COMPILE consortium

COntinuous **M**onitoring of **P**ooled **I**nternational Trials of Conva**LE**scent Plasma for COVID-19

Randomized trials, data from non-ICU patients only

Start 06.2021, 7 trials joined

Recruitment in 7 trials ended March 2021

Thanks to Andrea Troxel, NYU Langone

JAMA | Original Investigation

Association of Convalescent Plasma Treatment With Clinical Outcomes in Patients With COVID-19

A Systematic Review and Meta-analysis

Perrine Janiaud, PhD; Cathrine Axfors, MD, PhD; Andreas M. Schmitt, MD; Viktoria Gloy, PhD; Fahim Ebrahimi, MD, MSc; Matthias Hepprich, MD; Emily R. Smith, ScD, MPH; Noah A. Haber, ScD; Nina Khanna, MD; David Moher, PhD; Steven N. Goodman, MD, PhD; John P. A. Ioannidis, MD, DSc; Lars G. Hemkens, MD, MPH

Want to read more?

JAMA. 2021;325(12):1185-1195. doi:10.1001/jama.2021.2747
Published online February 26, 2021.

Conclusion:

When patients need to be admitted to a hospital for COVID-19

- Antibody formation has started in majority and will start very soon in the rest

  => Viral replication will be controlled around or soon after admission in most patients

- Proinflammatory procoagulant state predominates

  => Antibody based therapy in unselected hospitalized patient population of limited value

  => Effect remains to be shown for in antibody negatives / early presenters / immunocompromised

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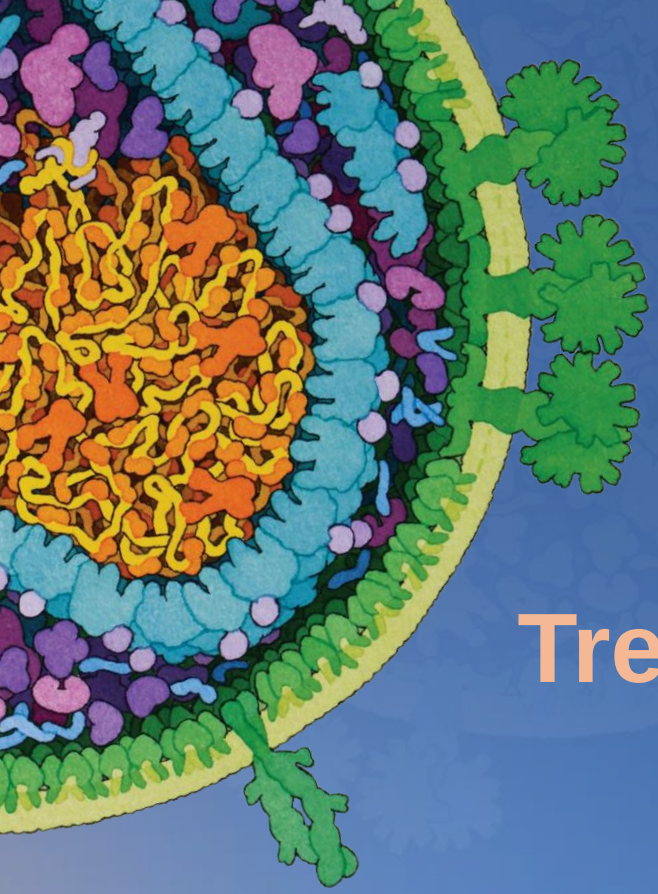
Why not close the books on antibody based therapy entirely?

Therapy:

Data from B-cell depleted patients suggest benefit
Hopefull sign in small RCT of very early Conv Plasma therapy
Phase 3 trials of monoclonal antibody-based therapy for early outpatient therapy
Phase 3 trials of Conv Plasma for high-risk outpatients with COVID19

Prevention in high risk patients

Syrian Hamster model : Human ConvP protects against COVID
Phase 3 trials of monoclonal antibody-based prevention
Phase 3 trials of Conv Plasma based prevention



SCIENCE SPOTLIGHT™

Treatment of COVID-19 with Convalescent Plasma in 23 B-cell Depleted Patients

Arvind Gharbharan, MD, MSc, Carlijn C.E. Jordans, MD, MSc, Adam A. Anas, MD, PhD, Susanne Bogers, MsC, Corine H. Geurts van Kessel, MD, PhD, Casper Rokx, MD, PhD, Bart J.A. Rijnders, MD, PhD

Disclosure:

Nothing to disclose

Erasmus University Medical Centre
Department of Internal Medicine, Section of Infectious Diseases
Rotterdam, the Netherlands

CROI 2021

Introduction

- Treatment with Convalescent plasma (ConVP) of B-cell depleted COVID-19 pts
  - Positive PCR and no SARS-CoV2 antibodies despite prolonged symptoms
  - Infusion of 300 or 600mL ConvP
    - PRNT50 at least 1:160 *or* in-house RBD ELISA with 10% highest titers

- Primary outcome: clinical recovery

  Secondary outcome: time until isolation could be lifted (PCR negative or 2xCt >30)

Results

- 61% male, median age 50y (Range 20-70)
- Rituximab (19), Blinatumomab (1), Obinutuzumab (1), XLA (1), Ocrelizumab (1)
- Lymphoma (10), auto-immune (8), CLL (2), B-ALL (1), MS (1)

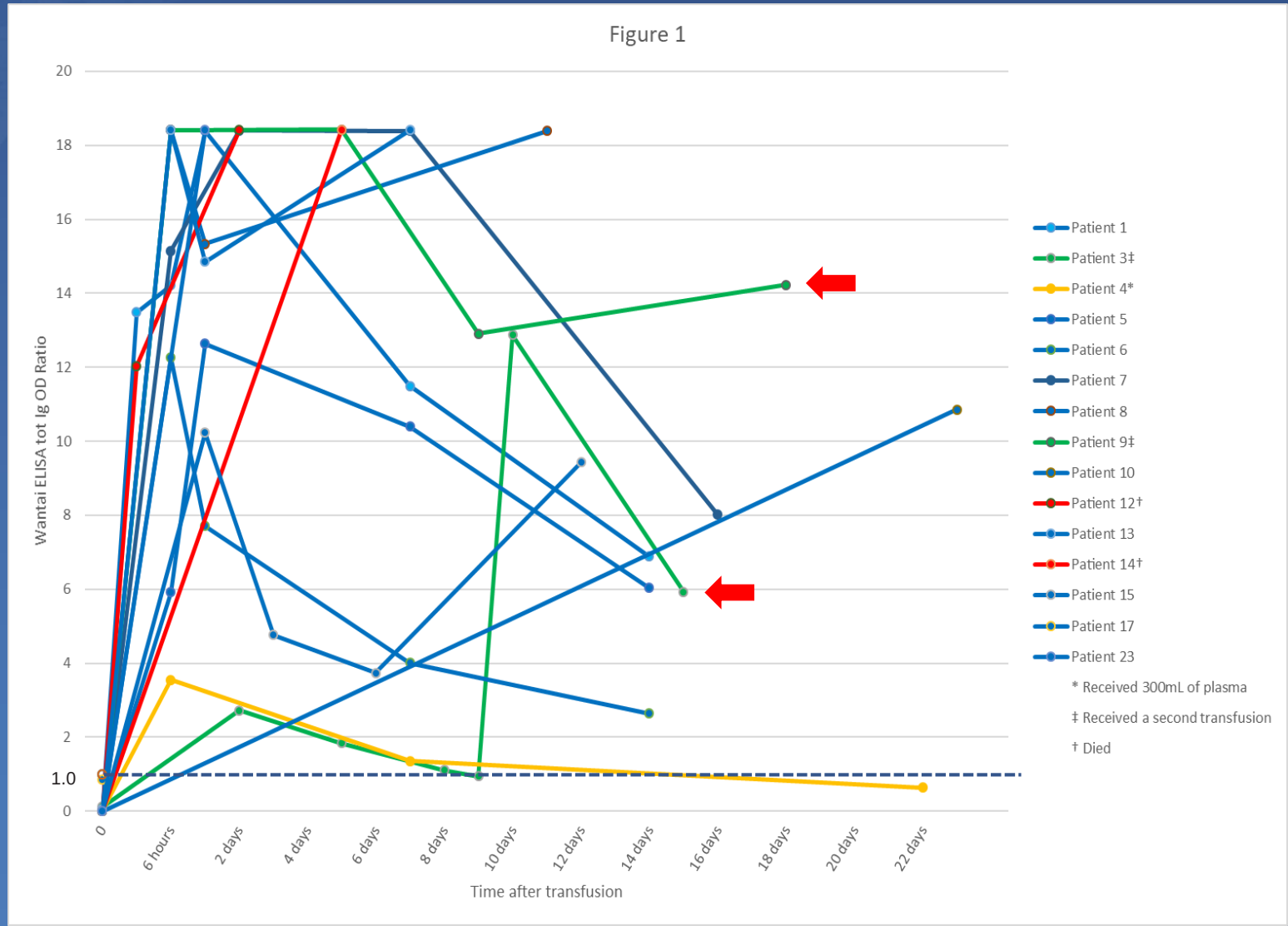
- Duration of symptoms before transfusion = **26 days** (IQR 17-35)
- Outpatient (6), Clinical ward (11), ICU (6)

- Outcome:
  - Clinical recovery in 20/23 patients : Typically prompt clinical improvement
  - 3 patients died 7, 8 and 13 days after transfusion
    - End stage refractory pulmonary fibrosis, relapsed lymphoma, 70 years and lymphoma
    - 2 on ICU at time of transfusion, 1 on clinical ward

  - PCR became negative in all 20 survivors
  - Time until isolation could be lifted = 10,5 days (IQR 6 – 17,5)

Results

- 17 pts received 600 mL ConvP
  - Patient 9 received a second transfusion of 600 mL (⬅)
- 6 pts received 300 mL ConvP
  - Patient 3 received second transfusion of 600 mL (⬅)
- All seroconverted



Conclusion

- Clinical recovery in the majority of patients
- The prompt clinical recovery in most patients suggests a therapeutic effect of convalescent plasma in B-cell depleted patients
- We suggest an initial dose of 600mL ConvP
  - Sufficient amount of neutralizing antibodies (top 10% of donors)
- Randomised clinical trials needed to confirm our observations
  - CoV-Early study for outpatients
  - COMPROMISE study for inpatients (Nanogam *plus)*

Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults

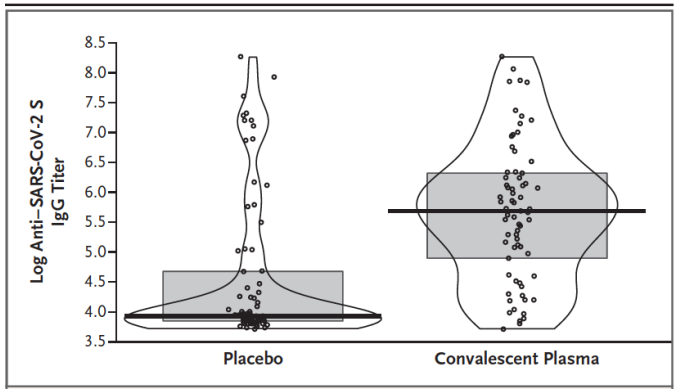
Population:
<72hrs of symptoms !
65y with comorbidity or 75y without comorbidity

Intervention:
250ml Conv or non-Conv Plasma

Primary endpoint:
- RR of 30 or more
- Room air saturation of 93% or less

Variable	Convalescent Plasma (N=80)	Placebo (N=80)
Demographic characteristics		
Age — yr	76.4±8.7	77.9±8.4
Time since onset of symptoms —	39.6±13.9	38.3±14.3

Antibody titers 24h after transfusion



R. Libster et al. New Eng J Med 2021

End Point	Convalescent Plasma (N=80)	Placebo (N=80)	Relative Risk (95% CI)
	no./total no. (%)		
Primary end point: severe respiratory disease	13/80 (16)	25/80 (31)	0.52 (0.29–0.94)
Secondary end points			
Life-threatening respiratory disease	4/80 (5)	10/80 (12)	0.40 (0.13–1.22)

Table 3. Primary End Point, According to Donor SARS-CoV-2 S IgG Titer.

Patient Group	Patients with Severe Respiratory Disease	Relative Risk (95% CI)	Relative Risk Reduction
	no./total no. (%)		*percent*
Placebo group	25/80 (31)	1.00	
Recipient of SARS-CoV-2 S IgG in donor plasma*			
At a titer at or above median concentration	3/36 (8)	0.27 (0.08–0.68)	73.3
At a titer below median concentration	9/42 (21)	0.69 (0.34–1.31)	31.4

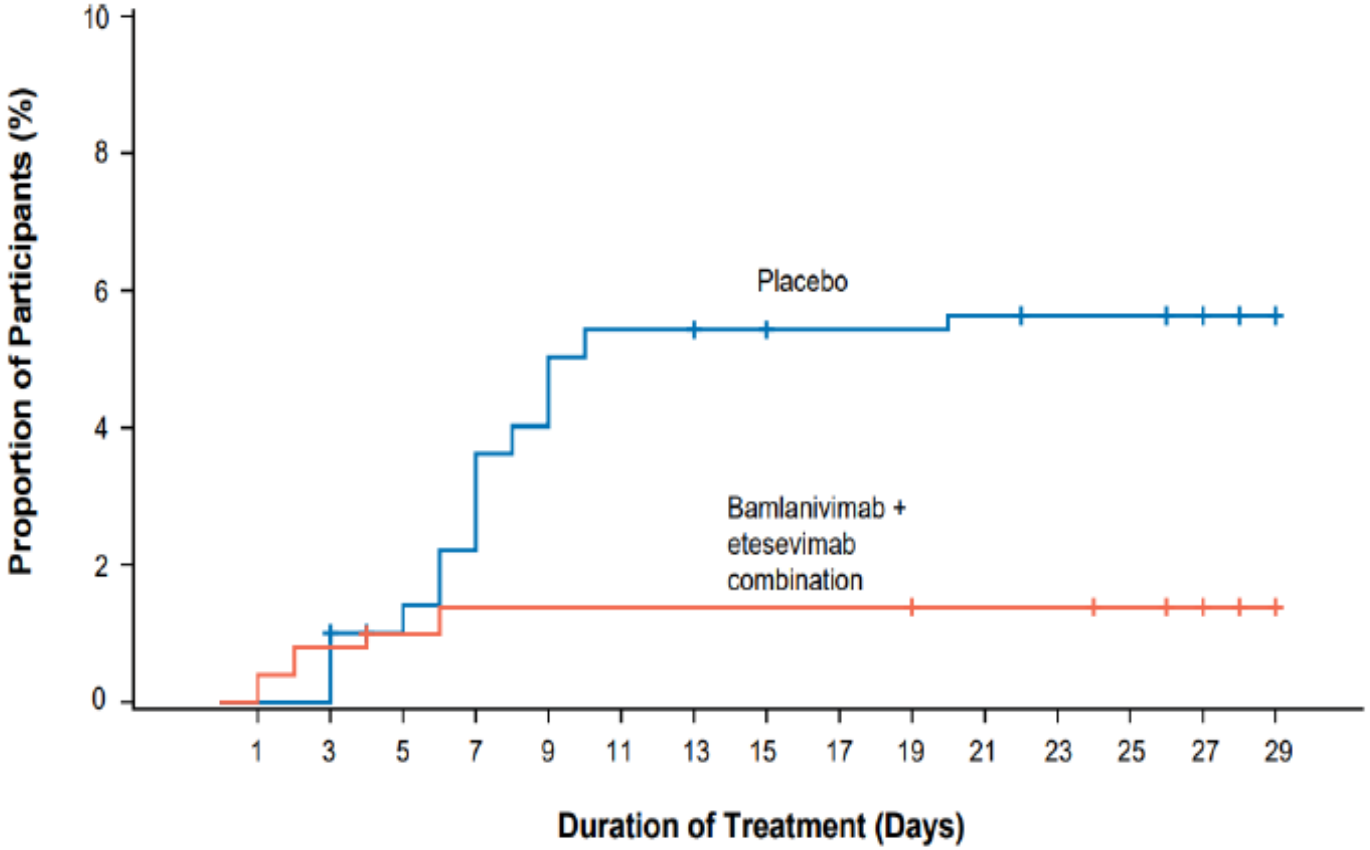
R. Libster et al. New Eng J Med 2021

Monoclonals *CROI March 2021* *Bamlanivumab + Etesevimab*

Phase 3: Patients presenting with mild-to-moderate COVID-19 within 3 days of their first positive test for SARS-CoV-2 were included

- The primary endpoint was COVID-19-related hospitalizations or any-cause death by Day 29, and was analyzed using logistic regression

	Placebo (N=517)	Bamlanivimab 2800 mg + Etesevimab 2800 mg (N=518)
Female†	50%	54%
Hispanic or Latino	30%	29%
Black or African American	8%	9%
Age (median)	56	57
Age ≥ 65	30%	32%
Body-mass index (mean)	33	34
Mild COVID-19	78%	77%
Moderate COVID-19	22%	23%
Duration of symptoms (days, mean)	4.2	4.1



Treatment	N	Events	Rate	*p*
Placebo	517	36	7.0%	-
Bamlanivimab 2800 mg + Etesevimab 2800 mg	518	11	2.1%	0.0004

ANY-CAUSE DEATHS

Treatment	N	Events	Rate
Placebo	517	10†	1.9%
Bamlanivimab 2800 mg + Etesevimab 2800 mg	518	0	0%

VIR-7831 (now GSK) Press release EMA fast track review

Monoclonal active against SARS1 and SARS2 (including variants of concern)

Inclusion Criteria:

- ≥ 55 years old OR 18 years with high risk of progression of COVID-19
- Not hospitalized and oxygen saturation ≥94% on room air
- COVID-19 symptoms for no more than 5 days

Interim analysis of Phase 3 COMET-ICE trial, which evaluated VIR-7831 as monotherapy

Study was stopped by DSMB after analysed of 583 randomised patients

85% (p=0.002) reduction in hospitalisation or death in those receiving VIR-7831

https://clinicaltrials.gov/ct2/show/NCT04545060

https://www.biorxiv.org/content/10.1101/2021.03.09.434607v1

Ongoing convalescent plasma / COVig trials to look out for

CSSC-001
USA, Boston, N=500
Prophylaxis after exposure

CP3O
USA
N=600 ER discharged
<8d of symptoms

CoV-Early
NL, Rotterdam-Leiden
N=690 outpatients
<8d of symptoms 50y +risk

COn-Vert
Spain
N=470 outpatients
<8d of symptoms, >50y

CSSC-004
USA
N=1344 outpatients
<8d 18y or older

COMPROMISE
NL, N=86, Immunocomp
Hospitalized AB negative
Nanogam *plus*

Fase ½ Nanogam *plus*
NL, N=104
SARS-2 AB negative after vaccination
Nanogam *plus* (n=80) Conv P (n=24)

Ongoing convalescent plasma / COVig trials to look out for

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Prophylaxis after exposure

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Nanogam *plus*

Fase ½ (dose finding)
NL, N=104
SARS-2 AB negative after vaccination
Nanogam *plus* (n=80) Conv P (n=24)

Ongoing convalescent plasma / COVig trials to look out for

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NL, N=86, Immunocomp
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Fase ½ Nanogam *plus*
NL, N=104
SARS-2 AB negative after vaccination
Nanogam *plus* (n=80) Conv P (n=24)

Last but not least: **COMPILE**$_{\textbf{home}}$

Pooling of CoV-Early and COn-Vert (n=800 recruited so far) and negotiations pending with CSSC-004
First interim end of May (n=600 complete follow-up)

Big thanks to many

Donors !

Media Campaign => Inbox: >3000 mails within 2 weeks from ***potential*** donors

=> but what are the useful donors?

Research is fun ?

Not always, but sometimes

Research is fun ?

Not always, but sometimes


Medical students

Thanks !

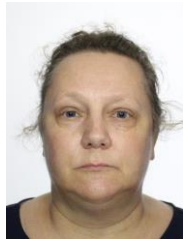










Casper Rokx
Peter te Boekhorst
Carlijn Jordans
Arvind Gharbharan
Rosanne Verwijs
Sammy Huygens

Statistics: G Papageorgiou
Viroscience: C Geurts B Haagmans, M Koopmans
Sanquin: F Swaneveld, V Novotny
Hematology: P te Boekhorst
Immunology: P Katsikis, Y Muller
HOVON / IT Erasmus MC

All the colleague-infectiologists and microbiologists: Giving me time for this project !

Ethics committee: For the unprecedented fast-track review

Backup slides

Compromise Study

Population

- COVID-19
- Admitted (or willing to be admitted for 1 day)
- Immunocompromised
  - B-cell depleted or B-cell insufficient

Randomized double blind

N=43 Nanogam$_{plus}$ 150 ml

N=43 Nanogam$_{regular}$ 150 ml

Only difference = Batch nr

B-cell inhibition related ICP

- Use of anti-CD19 or -CD20 directed antibody therapy in 6 months prior to inclusion.
- Previous or current treatment with drugs that significantly impair B cell function (e.g. ibrutinib, venetoclax, acalabrutinib, idelalisib etc) within 6 months prior to inclusion

Other immunosuppression/treatment related ICP

- Patients treated with bendamustine, purine analogues or anti-thymocyte globulin within 6 months prior to inclusion.
- Solid organ transplant patients that are taking systemic immunosuppressive drugs from at least three pharmacological classes.

Cellular therapy related ICP

- Allogeneic hematopoietic stem cell transplant (HSCT) in 12 months prior to inclusion.
- HSCT for which systemic therapy against graft-versus-host-disease is used.
- Recipient of CAR-T cells < 2 years prior to inclusion.

Disease related ICP

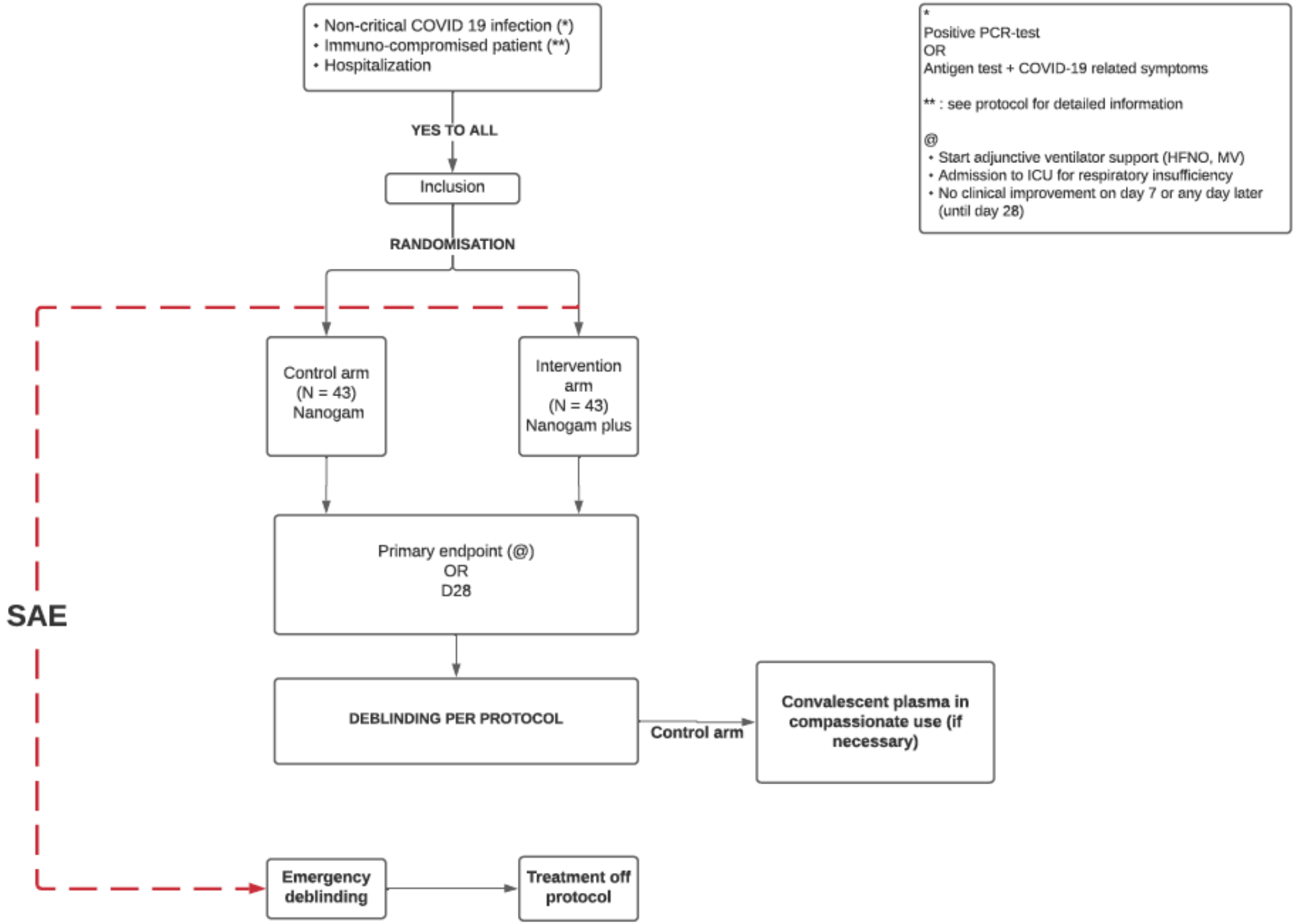
- Chronic B-cell leukemia´s: CLL, HCL, PLL, multiple myeloma, Waldenströms macroglobulinemia

Congenital ICP

- Congenital disorder resulting in severe B-cell dysfunction or depletion requiring immunoglobulin suppletion (e.g. agammaglobulinemia).

FULL PROTOCOL

SCAN ME


• Non-critical COVID 19 infection (*)
• Immuno-compromised patient (**)
• Hospitalization
YES TO ALL
Inclusion
RANDOMISATION
Control arm
(N = 43)
Nanogam
Intervention
arm
(N = 43)
Nanogam plus
Primary endpoint (@)
OR
D28
DEBLINDING PER PROTOCOL
Control arm
Convalescent plasma in compassionate use (if necessary)
SAE
Emergency deblinding
Treatment off protocol
*
Positive PCR-test
OR
Antigen test + COVID-19 related symptoms
** : see protocol for detailed information
@
• Start adjunctive ventilator support (HFNO, MV)
• Admission to ICU for respiratory insufficiency
• No clinical improvement on day 7 or any day later (until day 28)

COVID trials as of April 15 2021

Outpatients with COVID, not immunocompromised and symptom duration <8 days

>49 years => COV-Early or monoclonal antibody study tel. +31 6 50 19 04 90 or 91

18-49 years => Monoclonal antibody study (symptoms <6d) tel. +31 6 50 19 04 90 or 91

(Arvind and Carlijn)

Immunocompromised with COVID19

Outpatient

<8d of symptoms => CoV-Early call 0650190490 or 91 (Arvind or Carlijn)

>7d of symptoms => Compromise call 0631135687 (Sammy) or Kliko2 or Bart

Hospitalized

Any duration of symptoms => Compromise call 0631135687 (Sammy) or Kliko2 or Bart

Vaccination non responders

2 or more weeks after last vaccination and SARS-CoV-2 Antibody test negative

=> ConvCog study mail Sammy (s.huygens@erasmusmc.nl) or call 0631135687

SARS-Cov-2 (COVID-19) Syrian Hamsters COVID model

Convalescent plasma from patients with PRNT50 >1:1280 was pooled

Treated with 500uL IP with undiluted plasma (>1:1280; high) and 1:10 diluted plasma (1:320 “low”)

Prophylactic treatment by IP injection 24h prior to challenge

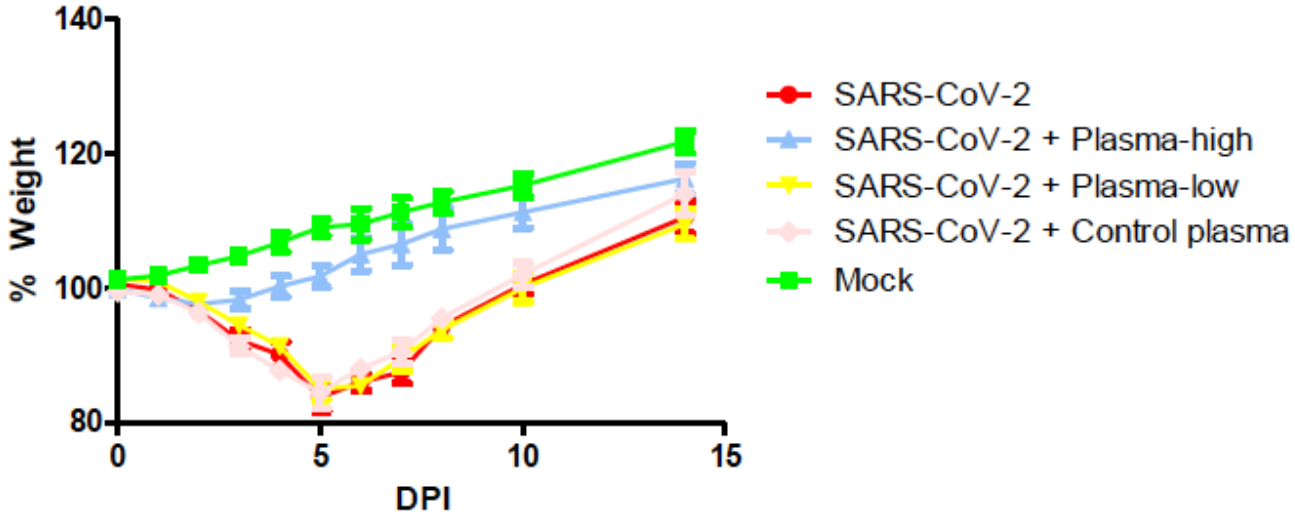
Intranasal challenge with SARS-CoV-2

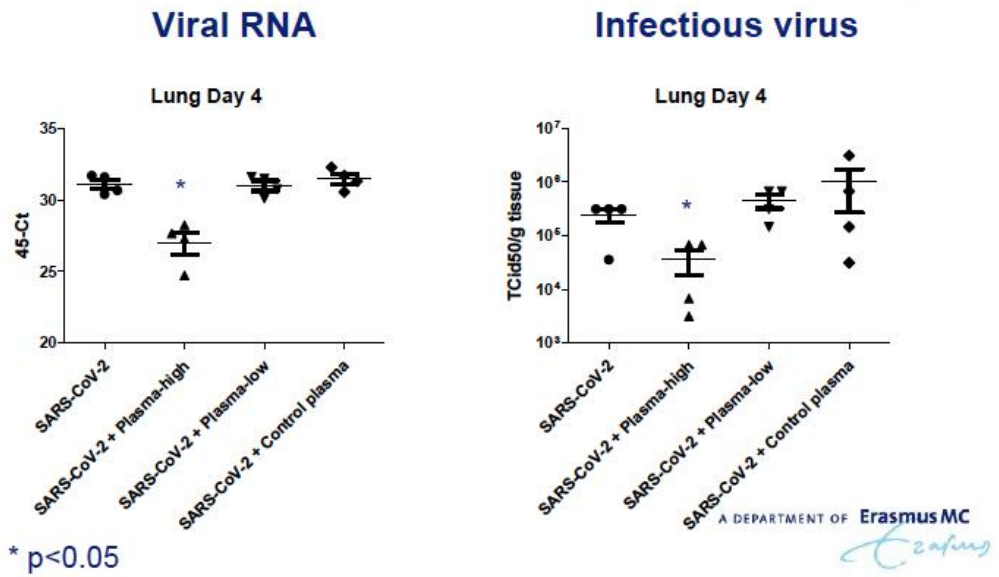
Daily weights, Nasal wash, throat and rectal swabs

Necropsies on day 4

Barry Rockx et al. MedRxiv, Erasmus MC

SARS-Cov-2 (COVID-19) Data from 2 very recent animal studie studies

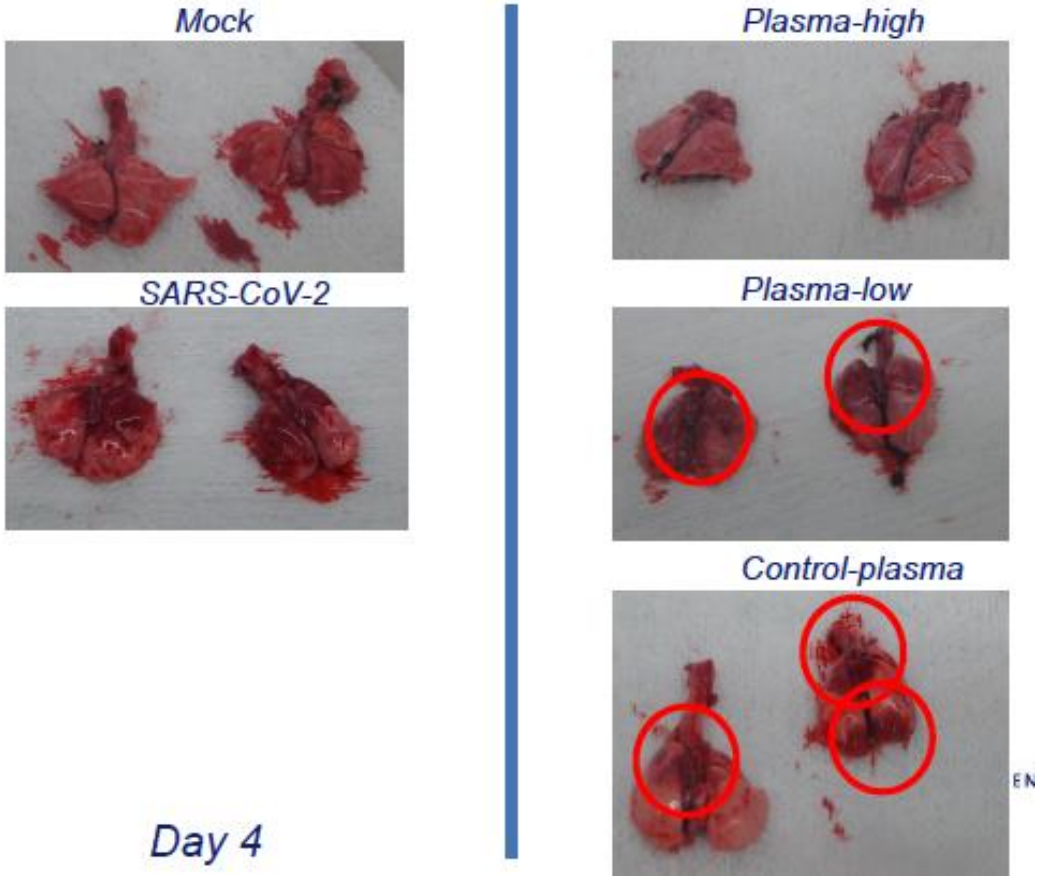




But no significant effect on higher airway shedding

SARS-Cov-2 (COVID-19) Data from 2 very recent animal studie studies

Gross lung lesions associated with SARS-CoV-2



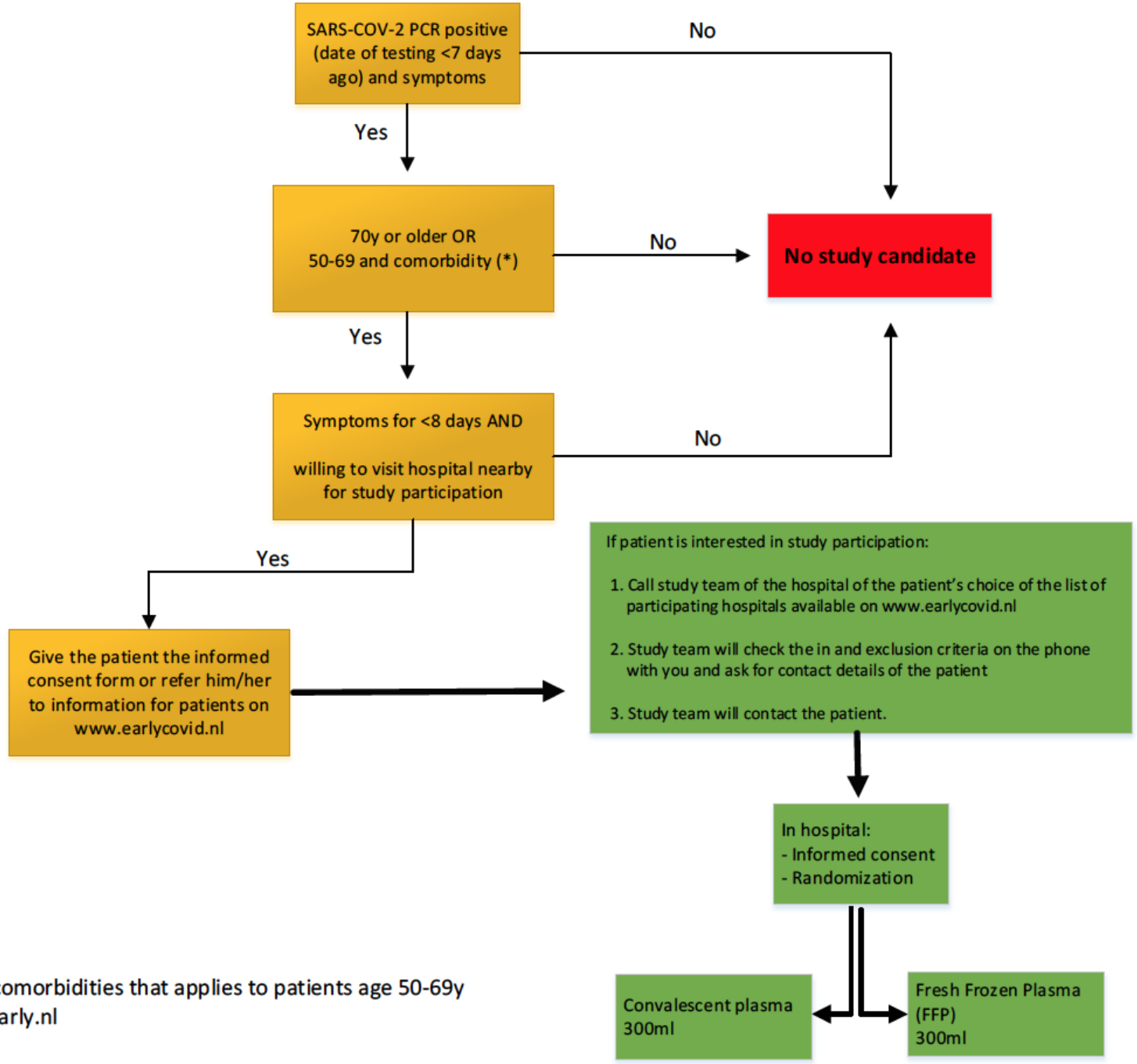
CoV-Early study

Early Convalescent Plasma Therapy for high-risk patients with COVID-19 in primary care

PROTOCOL

Version	:	3.0
Date	:	5 November 2020
Principal investigator EMC	:	Bart Rijnders and Casper Rokx
Principal investigator LUMC	:	Jaap Jan Zwaginga
Sponsor	:	Erasmus MC
Funder	:	ZONMW
Clinical research organization	:	HOVON Data Center
ID	:	NL74972.078.20
Clinicaltrials.gov	:	NCT04589949

CoV-Early design



(*) For the list of comorbidities that applies to patients age 50-69y see www.covearly.nl

Study design	This trial is a nationwide multicenter, double blind, randomized controlled trial in the Netherlands. Patients will be randomized between the transfusion of 300mL of convP versus regular fresh frozen plasma (FFP).
Patient population	Patients with PCR confirmed COVID disease with less than 8 days of symptoms, age 70 or older or 50-69 years with at least 1 additional risk factor for severe COVID-19 are eligible. A total of 690 patients will be included. Expected duration of accrual: 18-24 months
Intervention	300mL of convP with a minimum level of neutralizing antibodies (see chapter 6). Duration of follow up :Day 28 for the primary endpoint

Age 70 or older OR

Age 50-69 PLUS one of the following clinical or lab-based risk factors

- Obesity with BMI 35 or higher
- Born as a male person
- Cardiac or pulmonary disease (e.g. atrial fibrillation, CAD, heart failure, COPD, asthma)
- History of neurological disease (e.g. stroke or any other chronic debilitating neurological disease)
- Diabetes for which medical therapy is needed
- Chronic kidney disease with GFR <60 ml/min
- Reumatic disease (e.g. reumatoid arthritis, Systemic lupus erythematosus, psoriatric artritis)
- Immunodeficiency (e.g. organ or allogeneic transplantation, systemic immunosuppressive drugs)
- Cancer not in complete remission for >1 year (excluding baso -or spinocellular skin cancers)
- Untreated HIV and CD4 T-cells <200/microliter
- Chronic liver disease (liver cirrhosis child pugh A/B/C or other disease leading to liver dysfunction)
- (CRP > 30 or SARS-CoV-2 RT-PCR Ct value <25)

Age 18-50

- Severily immunocompromised (inherited deficiency OR HD oral corticosteroids, transplantation)

Inclusion criteria

A subject must meet all of the following criteria

- RT-PCR-confirmed COVID-19
- Symptomatic (e.g fatigue, fever, cough, dyspnoe, loss of taste or smell, diarrhea, falls or confusion)
- 70 years or older OR 50-69 years and 1 or more of the risk factors described in Appendix A

Exclusion criteria

- Life expectancy <28 days in the opinion of the treating physician
- Patient or legal representative is unable to provide written informed consent
- Symptomatic for 8 days or more
- Known IgA deficiency or history of transfusion-related acute lung injury or IgA

Primary Endpoint

Highest disease status on the 5-point ordinal disease severity scale in the 28 days following transfusion of convP versus FFP

Disease status is measured with a 5-point ordinal scale in which

1 = Fully recovered (no symptoms) within 7 days after transfusion

2 = Continued symptoms attributable to COVID-19 on day 7 after transfusion

3 = Admitted to hospital but no invasive ventilation needed

4 = Admitted to hospital and invasive ventilation needed

5 = Death

How to contact the study team for questions

mail us on covearly.study@erasmusmc.nl

If urgent (e.g. check if patient is eligible): *Call Erasmus MC (0107040704) and ask for one of the study team members. They can link you to local hospital study team*

How do patients get in contact with the study site?

www.coronaplasmastudie.nl

www.cov-early.nl

⇒ Patient fills in the contact form

⇒ We contact the patient, check criteria and plan day 1 (transfusion)