

Tocilizumab Treatment for Cytokine Release Syndrome in Hospitalized Patients With Coronavirus Disease 2019

Survival and Clinical Outcomes

Christina C. Price, MD; Frederick L. Altice, MD; Yu Shyr, PhD; Alan Koff, MBBS; Lauren Pischel, MD; George Goshua, MD; Marwan M. Azar, MD; Dayna Mcmanus, PharmD; Sheau-Chiann Chen, PhD; Shana E. Gleeson, MD; Clemente J. Britto, MD; Veronica Azmy, MD; Kelsey Kaman, MD; David C. Gaston, MD, PhD; Matthew Davis, PharmD; Trisha Burrello, MS; Zachary Harris, MD; Merceditas S. Villanueva, MD; Lydia Aoun-Barakat, MD; Insoo Kang, MD; Stuart Seropian, MD; Geoffrey Chupp, MD; Richard Bucala, MD, PhD; Naftali Kaminski, MD; Alfred I. Lee, MD, PhD; Patricia Mucci LoRusso, DO, PhD; Jeffrey E. Topal, MD; Charles Dela Cruz, MD, PhD; and Maricar Malinis, MD

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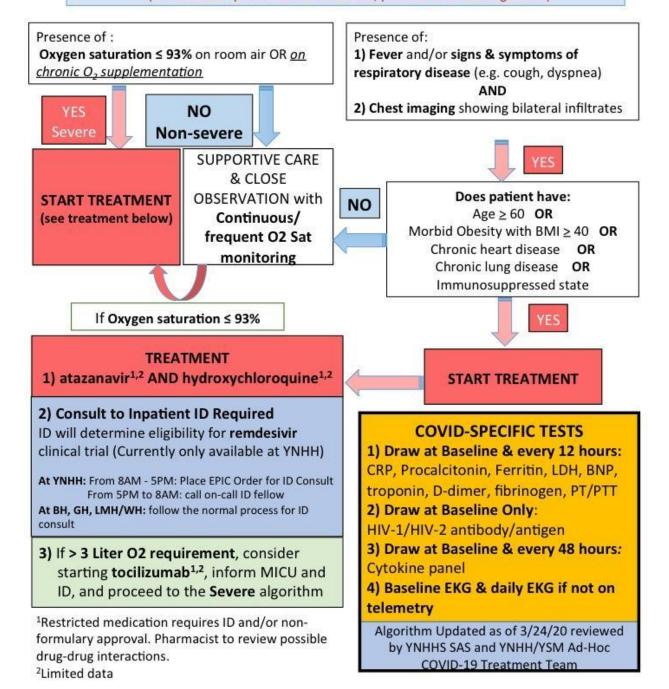
e-Appendix 1: Initial YNHH COVID-19 Treatment algorithm*

YNHHS Treatment Algorithm for Hospitalized PATIENT with Non-Critical* COVID-19

Disclaimer: There are no FDA-approved treatments for COVID-19, supportive care is standard of care. Limited treatment data are available & clinical judgment is warranted.

PATIENT with confirmed POSITIVE SARS-CoV-2 by PCR

*(If mechanically ventilated or on ECMO, proceed to Severe algorithm)



YNHHS Treatment Algorithm for Hospitalized PATIENTS with Critical COVID-19

Disclaimer: There are no FDA-approved treatments for COVID-19, supportive care is standard of care. Limited treatment data are available & clinical judgment is warranted.

Respiratory failure with Mechanical ventilation (including ECMO) PLUS confirmed POSITIVE SARS-CoV-2 by PCR

TREATMENT

atazanavir1,2 & hydroxychloroquine1,2



Consult Inpatient Infectious Diseases to consider other therapies

At YNHH: From 8AM - 5PM: Place EPIC Order for ID Consult

From 5PM to 8AM: call on-call ID fellow
At BH, GH, LMH/WH: follow the normal process

for ID consult

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Consider tocilizumab x 1 dose

(Additional doses determined by clinical response given the drug's long half-life in consultation with ID, pharmacy, & critical care)

Remdesivir is no longer available for compassionate use. Gilead is transitioning to a clinical trial and extended access program which is actively being pursued. Cases will be reviewed for clinical trial candidacy.

COVID-SPECIFIC TESTS

1) Draw at Baseline & every 12 hours: CRP, Procalcitonin, Ferritin, LDH, BNP troponin, D-dimer, fibrinogen, PT/PTT

2) Draw at Baseline Only: HIV-1/HIV-2 antibody/antigen

- 3) Draw at Baseline & every 48 hours: Cytokine panel
- 4) Baseline EKG & daily EKG if not on telemetry

Monitor patients closely for digital and nasal tip ischemia

Monitor electrolytes:
Replete Mg >2, K >4
Follow EKG/Telemetry closely for
QTc Prolongation

Caution combining QTc prolonging medications

Algorithm Updated as of 3/24/20 reviewed by YNHHS SAS and YNHH/YSM Ad-Hoc COVID-19 Treatment Team

¹Restricted medication requires ID and/or nonformulary approval. Pharmacist to review possible drug-drug interactions ²Limited data

^{*} Patients who began to develop findings of CRS, evidenced by increased oxygenation needs, markedly elevated or increasing hsCRP levels, could also receive tocilizumab.



e-Appendix 2: Risk factors Supplemental and definition of Immunosuppression

Age <u>></u>	60,	BMI	>	40
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Hypertension

Diabetes

Chronic heart disease

Chronic lung disease

Immunosuppressed: Cancer treatment within 1 year, the use of immunosuppressive drugs (biologics, chronic prednisone ≥20mg daily), solid organ transplant, bone marrow transplantation, HIV/AIDS (regardless of CD4 count), leukemia, lymphoma, SLE, or vasculitis.

e-Appendix 3: Treatment protocol laboratory panel and clinical monitoring

The COVID-19 lab panel consisted of hsCRP (high sensitivity C-reactive protein), procalcitonin, ferritin, troponin, lactate dehydrogenase, pro-brain natriuretic peptide, fibrinogen and prothrombin time every 12 hours. Additionally, a baseline HIV test was ordered given the use of a single anti-retroviral agent, and a cytokine panel was drawn every 48 hours. Cytokine panel included soluble Interleukin 2 Receptor (sIL2R or CD25), Interleukin 12, Interferon gamma, Interleukin 4, Interleukin 5, Interleukin 10, Interleukin 13, Interleukin 1 beta, Interleukin 6, Interleukin 8, Tumor Necrosis Factor-alpha, Interleukin 2, and Interleukin 17. Cytokine panel tests were performed via a quantitative multiplex bead assay by a CLIA-certified diagnostic lab in Salt Lake City, Utah. Lower limit of detection was 5pg/mL. Laboratory values were included in the analysis up to twice daily (if available) if they were twelve hours apart +/- two hours; if not then a single daily value was recorded. Chest radiographs were repeated only for worsening clinical status to reduce increased exposure.

e-Appendix 4. Oxygen data entry and definitions

The admission oxygen saturation on room air from the nursing triage note was utilized. In cases where patients arrived with a new supplemental oxygen, the oxygen saturation reported by emergency medical services (EMS) was used. Patients arriving from EMS already on supplemental oxygen reporting values such as "80's on room air" could not be included for this one variable; all of these patients had reported oxygen saturations of less than 90%. Patients on chronic oxygen therapy were included in the analysis of admission oxygen saturations so long as their oxygen requirement was at their baseline at the time of measurement. Nasal cannula values with 0.5L measurements were rounded up to the nearest liter.

Scale	Oxygen Requirement
0	Room Air
1	1L nasal cannula
2	2L nasal cannula
3	3L nasal cannula
4	4L nasal cannula
5	5L nasal cannula
6	≥6L nasal cannula OR Venti mask
7	Non-rebreather
8	High flow nasal cannula OR non-invasive positive pressure ventilation
9	Intubated with FiO2 <50% and PEEP ≤5 cmH ₂ 0
10	Intubated with FiO2 ≥50% but <70% OR PEEP >5 but <15 cmH ₂ 0
11	Intubated with FiO2 ≥70% but <100% OR PEEP ≥15 but <20 cmH ₂ 0
12	Intubated with FiO2 100% OR PEEP ≥20 cmH ₂ 0
13	Extracorporeal membrane oxygenation (ECMO)

e-Table 1: Survival at 7, 14 and 21 days

	Overall	Non-Severe	Severe
Entire Sample	N=239	N=135	N=134
7 days	92 (88, 96)	97 (95-100)	86 (79, 93)
14 days	86 (81, 91)	93 (88, 99)	78 (69, 87)
21 days	81 (75, 88)	91 (84, 98)	71 (61, 83)
Tocilizumab Subgroup	N=153	N=59	N=194
7 days	94 (90, 98)	98 (95,100)	91 (85, 97)
14 days	86 (80, 93)	92 (83, 100)	83 (75, 92)
21 days	82 (74, 90)	92 (83, 100)	75 (66, 88)
No Tocililzumab Subgroup	N=86	N=76	N=10
7 days	89 (83, 97)	NA	NA
14 days	87 (78, 96)	NA	NA
21 days	81 (69, 95)	NA	NA
Mechanically Ventilated Subgroup	N=53	N=7	N=46
7 day	78 (68, 91)	NA	NA
14 day	72 (60, 86)	NA	NA
21 day	67 (55, 82)	NA	NA



e-Table 2: Clinical consequences before and after tocilizumab administration, stratified by disease severity (N=153)

		Non-severe			Severe	
		(N=59)			(N=94)	
		-			-	P
Variables	N	Statistics	P Value	N	Statistics	Value
Maximum Temperature Change,		-1.35			-1.35	<0.001
median (95%CI)	33	(-1.65, -1)	<0.001 a	76	(-1-6, -1-1)	a
Pre-TCZ Temperature °C,		38.8			39.18	
median (IQR)	59	(38-2, 39		94	(38·35, 39·4)	
Post-TCZ Temperature °C,		37∙2			37.37	
median (IQR)	33	(37, 37.	56)	76	(37·1, 38·23)	
D-Dimer Change, median		0.67			1.09	<0.001
(95%CI)	47	(0.31, 1.3)	<0·001 a	82	(0.62, 1.9)	a
Pre-TCZ D-Dimer, mg/L FEU,		0.94			0.98	
mean, median (IQR)	57	(0.56, 1.	35)	87	(0.62, 1.89)	
Post-TCZD-Dimer mg/L FEU		1.53			1.71	
mean, median (IQR)	47	(0.71, 3.	(33)	82	(0.99, 4.62)	
Absolute Lymphocyte Count	47	0.03	0.54	7.0	0.21	<0.001
Change 1, mean median (95%CI)	47	(-0.07, 0.15)	0.54₃	79	(0.13, 0.29)	a
Pre-TCZ Absolute Lymphocyte		4.04			0.0	
Count 1000/microL, mean,	F-7	1.01		00	0.9	
median (IQR)	57	(0.75, 1	.·4)	89	(0.7, 1.2)	
Post-TCZ Absolute Lymphocyte		1 17			1 11	
Count 1000/microL, mean,	47	1.17		79	1.11	
median (IQR)	47	(0·74, 1· -15·1	159) 	/9	(0·86, 1·42) -19·15	<0.001
hsCRP Change, median (95%CI)	49	(-24·5, -5·4)	0·001a	82	(-28·35, -10·6)	
Pre-TCZ hsCRP mg/L max,	49	131.9		02	137.75	a
median (IQR)	59	(84.8, 16		94	(102.15, 218.15)	
Post-TCZ hsCRP mg/L max,	39	113.7		34	103.2	
median (IQR)	49	(74.9, 15		82	(70.5, 188.62)	
IL-6 Change, mean median	7.7	103·12		02	136.8	<0.001
(95%CI)	26	(66·5, 165·5)	<0.001 a	62	(99.0, 179.6)	a
Pre-TCZi IL-6 pg/ml, mean,	20	15.67		02	19	a
median (IQR)	53	(6, 34		86	(7, 74)	
Post-TCZ IL-6 pg/ml, mean,	- 55	105.7		"	146-62	
median (IQR)	26	(82.95, 17		62	(64·12, 254·88)	
Change in sIL2R, mean median		338-6			354-2	<0.001
(95%CI)	44	(186.6, 521.8)	<0.001 a	77	(220.2, 490.23)	a
Pre-TCZ sIL2R pg/ml, mean,		849.6			1114-3	-
median (IQR)	56	(528-3, 14		84	(783.9, 1710.5)	
Post-TCZ sIL2R pg/ml, mean,		,	,		1416-25	
median (IQR)	44	1245 (802.75	5, 1973)	77	(1041, 2081)	
Chest radiograph findings at 14		•				
days, No· (%)	129					<u> </u>
Improved		36 (75)	0·22 a		50 (62)	0·22 a
Unchanged		6 (12)			11 (14)	
Worse		6 (12)			20 (25)	
- Wilcovon signed-rank test TC7-t	111					

a Wilcoxon signed-rank test, TCZ=tocilizumab, FEU= Fibrinogen equivalent units, sIL2R=Soluble interleukin 2 receptor (CD25), TCZ=tocilizumab



e-Table 3: Safety profile of tocilizumab before and after treatment (N=153)

Variable	Pre-Treatment	
	No· (%)	No· (%)
Absolute neutrophil count (cells/mL), N=150		
≤500	2 (1)	6 (4)
Alanine aminotransferase (ALT), N=131		
Grade 0	87 (62)	43 (31)
Grade 1	47 (33)	52 (37)
Grade 2	4 (3)	21 (15)
Grade 3	3 (2)	23 (17)
Grade 4	0 (0)	0 (0)
Aspartate aminotransferase (AST), N=130		
Grade 0	25 (18)	9 (7)
Grade 1	100 (71)	84 (61)
Grade 2	12 (9)	23 (17)
Grade 3	4 (3)	21 (15)
Grade 4	0 (0)	0 (0)
Bacteremia, N=111		4 (4)

Grading system: 0 = within the normal range, 1 = within 3 times the upper limit of normal, 2 = 3-5 times the upper limit of normal, 3 = greater than 5 times the upper limit of normal, 4 = 10 times the upper limits of normal