

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

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Table S1. The BACC Bay Tocilizumab Trial Group

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Table S2. Ordinal Clinical Improvement Scale

Clinical Improvement Scale	
1	Discharged (or "ready for discharge" as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or \leq 2L supplemental oxygen)
2	Non-ICU hospital ward (or "ready for hospital ward") not requiring supplemental oxygen
3	Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen
4	ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen
5	ICU, requiring intubation and mechanical ventilation
6	ICU, requiring ECMO or mechanical ventilation and additional organ support (e.g. vasopressors, renal replacement therapy)
7	Death

Table S3. Change in inflammatory marker levels by treatment arm.

Marker	Estimated change per day		Difference (95% CI)
	Tocilizumab	Placebo	
C-reactive protein	-0.238	-0.092	-0.146 (-0.166, -0.125)
D-dimer	-0.001	0.008	-0.009 (-0.023, 0.004)
Ferritin	-0.059	-0.031	-0.028 (-0.038, -0.018)
Lactate dehydrogenase	-0.011	-0.018	0.006 (0.000, 0.012)
Serum IL-6	0.041	-0.081	0.122 (0.084, 0.162)

Table S3 demonstrates the changes over time in patients' serum C-reactive protein, ferritin, interleukin-6, lactate dehydrogenase, and d-dimer concentrations. C-reactive protein and ferritin levels decreased at a faster rate in patients in the tocilizumab group compared to the placebo group. Serum IL-6 levels increased with time in the tocilizumab group but decreased in the placebo group. In contrast, LDH levels decreased faster in patients in the placebo group. Changes in d-dimer concentrations were similar between the two groups. All markers were log-transformed prior to analysis. The estimated change is the change in the mean of the log-transformed outcome per day.

Table S4. Sub-Group Effects Of Tocilizumab By Baseline Serum IL-6 Concentration

Characteristic	Hazard ratio (95% CI) in subgroup	Interaction p-value
Age		0.75
> 65 years	0.65 (0.22, 1.92)	
≤ 65 years	0.63 (0.17, 2.37)	
Sex		0.92
Male	0.62 (0.21, 1.88)	
Female	0.63 (0.16, 2.47)	
Ethnicity		0.52
Hispanic or Latino	1.36 (0.25, 7.39)	
Not Hispanic or Latino	0.67 (0.25, 1.82)	
Obesity		0.81
BMI ≥ 30 kg/m ²	0.56 (0.17, 1.82)	
BMI < 30 kg/m ²	0.58 (0.17, 2.02)	
Diabetes		0.82
Yes	0.70 (0.20, 2.52)	
No	0.92 (0.28, 3.01)	
Serum IL-6		0.88
> 40 pg/ml	0.77 (0.24, 2.42)	
≤ 40 pg/ml	0.41 (0.11, 1.58)	
		0.25
> 24.4 pg/ml	0.95 (0.37, 2.42)	
≤ 24.4 pg/ml	0.24 (0.02, 2.43)	
Received remdesivir		0.51
Yes	0.56 (0.16, 1.88)	
No	0.88 (0.29, 2.65)	

The results imply the possibility of a reduction in risk of mechanical ventilation or death by tocilizumab among patients with serum IL-6 **less than** the median value at baseline, but the width of the confidence intervals precludes any definitive conclusion regarding impact of tocilizumab in that subgroup.

Table S5. Detailed description of Serious Adverse Events.

Tocilizumab Group

RECORD_ID	Type of adverse event	Grade	Relatedness
BMC-008	Other	3	Unrelated
BMC-010	Other	2	Unrelated
BMC-010	Other	2	Unrelated
BMC-014	Other	3	Related
BMC-014	AST elevated	1	Possibly
BMC-014	ALT elevated	1	Possibly
BMC-017	Neutrophil count decreased	4	Related
BMC-018	Neutrophil count decreased	3	Related
BMC-020	Other	3	Unrelated
BMC-023	Infection	3	Unrelated
BMC-023	Other	3	Unrelated
BMC-023	Other	4	Unrelated
BWH-002	Other	3	Unrelated
BWH-002	Other	2	Unrelated
BWH-002	Other	2	Unrelated
BWH-006	Death	5	Unrelated
BWH-023	Arterial ischemia	3	Unrelated
BWH-023	Death	5	Unrelated
MGH-016	Death	5	Unrelated
MGH-029	Death	5	Possibly
MGH-034	Other	3	Unrelated
MGH-041	Death	5	Unrelated
MGH-043	Infection	3	Possibly
MGH-069	Other	2	Unrelated
MGH-072	Death	5	Unrelated
NSMC-002	Infection	3	Possibly
NSMC-018	Death	5	Unrelated

RECORD_ID	Type of adverse event	Grade	Relatedness
NSMC-020	Stroke	3	Unrelated
NSMC-036	DVT	2	Unrelated
NSMC-046	Death	5	Possibly
NSMC-047	Death	5	Unrelated
NSMC-050	DVT	3	Unrelated
NSMC-051	Stroke	2	Unrelated
NSMC-054	Infection	3	Possibly
NSMC-063	PE	3	Possibly
NSMC-066	Other	3	Unrelated

Placebo Group

RECORD_ID	Type of adverse event	Grade	Relatedness
BILH-006	Infection	3	Unrelated
BILH-006	Death	5	Unrelated
BMC-009	Seizure	4	Unrelated
BMC-009	Infection	3	Related
BMC-009	Other	3	Unrelated
BMC-009	Other	3	Unrelated
BMC-009	Other	3	Unrelated
BMC-009	Other	3	Unrelated
BMC-019	Other	2	Unrelated
BMC-019	Other	3	Unrelated
BMC-019	Other	3	Unrelated
BMC-019	Other	2	Unrelated
BMC-019	Other	2	Unrelated
BMC-019	Infection	3	Related
BMC-019	Other	4	Unrelated
BMC-019	Other	2	Unrelated
BMC-019	Other	3	Unrelated
BMC-025	Other	3	Unrelated
BMC-025	Other	2	Unrelated

RECORD_ID	Type of adverse event	Grade	Relatedness
BMC-025	Other	3	Unrelated
BMC-025	Other	3	Unrelated
BMC-025	DVT	3	Unrelated
BMC-025	Other	2	Unrelated
MGH-017	Other	3	Unrelated
MGH-048	Infection	3	Possibly
MGH-057	Myocardial infarction	3	Unrelated
MGH-057	DVT	2	Unrelated
MGH-057	Bleeding	3	Unrelated
MGH-057	Infection	3	Unrelated
MGH-057	Other	3	Unrelated
MGH-057	Infection	3	Unrelated
MGH-073	AST elevated	4	Unrelated
MGH-073	ALT elevated	3	Unrelated
NSMC-011	Death	5	Unrelated
NSMC-028	PE	3	Unrelated
NSMC-065	PE	3	Unrelated
NSMC-065	Death	5	Unrelated
NSMC-070	Death	5	Unrelated

Table S6. List of Other Adverse Events Grouped by Treatment Arm and Severity.

Treatment arm=Tocilizumab SAE?=Yes

RECORD_ID	Description of adverse event	SAE?	Grade	Relatedness
BMC-008	Continued anorexia - patient continues inpatient due to refusal of food and IV medications - prolongation of hospitalization due to anorexia and not COVID	Yes	3	Unrelated
BMC-010	Hypoxia	Yes	2	Unrelated
BMC-010	Orthostatic hypotension after standing up - BP 79/60. IV fluid bolus given with BP back to 120s again. As a note patient has low BP at baseline - .CTCAE grade 2	Yes	2	Unrelated
BMC-014	Febrile Neutropenia	Yes	3	Related
BMC-020	Hypoxia - increase in O2 requirement from 4L to 15L (Grade 3)	Yes	3	Unrelated
BMC-023	Elevated PTT	Yes	3	Unrelated
BMC-023	Cardiogenic Shock	Yes	4	Unrelated
BWH-002	hypotension/ neutropenic shock	Yes	3	Unrelated
BWH-002	Low output from nephrostomy tube	Yes	2	Unrelated
BWH-002	Hypotension	Yes	2	Unrelated
MGH-034	Patient re-hospitalized because dialysis could not be arranged any other way	Yes	3	Unrelated
MGH-069	Hip fracture requiring hospitalization	Yes	2	Unrelated
NSMC-066	Pulmonary Fibrosis	Yes	3	Unrelated

Treatment arm=Tocilizumab SAE?=No

RECORD_ID	Description of adverse event	SAE?	Grade	Relatedness
BMC-001	Acute kidney injury (including elevated creatinine, decreased GFR)	No	2	Unrelated
BMC-004	Conjunctivitis	No	1	Possibly
BMC-005	decreased wbc count	No	3	Possibly
BMC-006	Bradycardia overnight - resolved, no intervention required	No	1	Unrelated
BMC-008	decreased WBC count	No	3	Possibly
BMC-008	Hypertension - BP of 152/87, asymptomatic, no intervention required	No	2	Possibly
BMC-008	decreased poly	No	.	Possibly
BMC-008	Diarrhea - 4 loose BMCTCAE Grade 2	No	2	Unrelated
BMC-012	Anemia	No	1	Unrelated

RECORD_ID	Description of adverse event	SAE?	Grade	Relatedness
BMC-014	increased alkaline phosphatase	No	1	Unrelated
BMC-017	Decreased WBC to 0.8	No	4	Possibly
BMC-017	Diarrhea - 4 watery non bloody bowel movements overnight and 1 this morning (Grade 2)	No	2	Possibly
BMC-020	Hypotension - BP 80's/40's, 1L IVF given(Grade 2)	No	2	Unrelated
BMC-020	Earache - given 650mg tylenol with relief(Grade 1)	No	1	Unrelated
BMC-022	Hypotension 70's/50's, 1L IVF given with good effect(Grade 2)	No	2	Unrelated
BMC-023	Bradycardia	No	1	Unrelated
BMC-023	worsening lower extremity wound	No	3	Unrelated
BMC-024	Hypertension - BP 170/93 (Grade 3)	No	3	Unrelated
BWH-006	Worsening confusion, Grade 2	No	2	Unrelated
MGH-003	Pruritic Rash	No	1	Unrelated
MGH-012	Syncope	No	1	Unrelated
MGH-020	Paroxysmal Atrial fibrillation. Reverted back to sinus rhythm in 10 min	No	1	Unrelated

Treatment arm=Placebo SAE?=Yes

RECORD_ID	Description of adverse event	SAE?	Grade	Relatedness
BMC-009	Tracheostomy	Yes	3	Unrelated
BMC-009	Tachypnea - patient experinced episode of tachypnea post bed bath(Grade 3)	Yes	3	Unrelated
BMC-009	Parasthesia - On 5/26 there was noted change in neurology exam with patient now not withdrawing to pain in upper extremity	Yes	3	Unrelated
BMC-009	Dysphagia resulting in PEG placement (Grade 3 SAE see below)	Yes	3	Unrelated
BMC-019	Hypoxia - worsening hypoxia with ambulation increased from 10L to 15L. Moved to step down for closer monitoring and remained on 15L satting at 95%. On 5/23 weaned to 8L with O2 sat >94%(Grade 2)	Yes	2	Unrelated
BMC-019	Worsening hypoxia - patient had grade 2 hypoxia on 5/22 which has increased to a grade 3 today.Today - hypoxia continued to worsen with further increasing oxygen requirements after desatting to the 70's and needed 15L NRB requiring inhaled NO and proningd	Yes	3	Unrelated
BMC-019	respiratory failure and intubation	Yes	3	Unrelated
BMC-019	Hypotension - thought to be due to sedation and vent setting(Grade 2)	Yes	2	Unrelated
BMC-019	Bradycardia to the 40's to the point of brief asystole(Grade 2 - serious)	Yes	2	Unrelated

RECORD_ID	Description of adverse event	SAE?	Grade	Relatedness
BMC-019	Respiratory Acidosis (Grade 4)	Yes	4	Unrelated
BMC-019	Hypothermia (Grade 2)	Yes	2	Unrelated
BMC-019	Elevated PTT	Yes	3	Unrelated
BMC-025	Subject had syncopal episode with hypotension while getting up to go to bathroom. Given 1 liter bolus IV fluid with improvement(Grade 3)	Yes	3	Unrelated
BMC-025	Hypoxia (Grade 2)	Yes	2	Unrelated
BMC-025	Anemia	Yes	3	Unrelated
BMC-025	Hypertension BP 194/95	Yes	3	Unrelated
BMC-025	Hospitalization for Syncope	Yes	2	Unrelated
MGH-017	Grade 3: Rash/allergic reaction (cause not clear. Not related to IP).	Yes	3	Unrelated
MGH-057	Renal injury, started 5/19, serious, expected, unrelated, requiring monitoring	Yes	3	Unrelated

Treatment arm=Placebo SAE?=No

RECORD_ID	Description of adverse event	SAE?	Grade	Relatedness
BMC-007	increased ALP	No	1	Unrelated
BMC-009	decreased WBC count	No	2	Possibly
BMC-009	Diarrhea x5 loose bowel movements (Grade 2)	No	2	Unrelated
BMC-016	Oropharyngeal Dysphagia - patient have difficulty swallowing in setting of COVID-19 and multi-focal PNA	No	2	Unrelated
BMC-019	decreased hgb	No	1	Unrelated
BMC-019	Hypotension - BP 75/50, 1L IVF given with good effect (Grade 2)	No	2	Unrelated
BMC-025	Sinus Tachycardia to 130's	No	1	Unrelated
BMC-025	Headache	No	1	Unrelated
BMC-025	Mild edema	No	1	Unrelated
BMC-025	Acute superficial thrombophlebitis	No	2	Unrelated
BMC-026	Mild LLE Edema	No	1	Unrelated
BMC-026	Dizziness	No	1	Unrelated
BMC-026	Constipation	No	1	Unrelated
BWH-003	intermittent afib with RVR with hypotension requiring IV rate control, hs-cTNT checked and downtrending from prior	No	2	Unrelated

RECORD_ID	Description of adverse event	SAE?	Grade	Relatedness
BWH-003	Remains quite delirious and confused. As of today able to grasp meaning of nursing instructions but still difficultly verbalizing - Grade III. Unrelated to drug - likely related to covid. This is prolonging hospitalization but present since admission	No	2	Unrelated
BWH-003	Ongoing atrial fibrillation with RVR-intermittent	No	2	Unrelated
BWH-003	Overnight had hypotension during HD and episode of epigastric pain, received 2u pRBC and underwent CT abdomen that demonstrated a new wall thickening of the sigmoid colon and rectum most likely representing proctocolitis. No pneumatosis, bowel perforate	No	2	Possibly
BWH-003	Ongoing elevated lactate with hypotension, echocardiogram today demonstrated worsening LV function with EF 15% with mod-severe MR. Severe RV dysfunction.	No	3	Unrelated
BWH-008	As prior, very poorly controlled BP Grade 3 - likely unrelated. Hyperglycemia better controlled tho still up to 380. Confusion and combative - a bit better today, still Grade 3. Also note CK elevated to 1760 on 4/30 (just noted) and coming down, today	No	2	Unrelated
MGH-057	hypertensive crisis	No	3	Unrelated
MGH-057	Anemia, Hgb down to 8.4 and transfused, expected, not serious	No	3	Unrelated
MGH-057	Mucus plugging, resolved with bronchoscopy Serious, expected, unrelated, required bronchoscopy	No	3	Unrelated
MGH-057	Anemia, Hct crept down to 22	No	3	Unrelated
NSMC-011	#AKI with AGMA and hyperkalemia	No	4	Unrelated
NSMC-035	hypomagnesemia with Mg 1.6; supplemented with Mg 8 beat run of non sustained V tach on telemetry, without symptoms; no treatment required.	No	1	Possibly
NSMC-057	Anemia Hgb < 7 requiring transfusion of pRBC's	No	2	Unrelated
NWH-017	FALL WITH BRUISE TO SHANK	No	1	Unrelated
NWH-017	FALL WITH ABRASION	No	1	Unrelated
NWH-017	VOMITING	No	1	Unrelated

