Reumatología Clínica

COVID02 - IL-6 serum levels predict severity and response to Tocilizumab in COVID-19: An observational study

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Resumen

Introduction: COVID-19 patients can develop a cytokine release syndrome leading to acute respiratory distress syndrome (ARDS) requiring invasive mechanical ventilation (IMV). Since interleukin-6 (IL-6) is a relevant cytokine in ARDS, its blockade with Tocilizumab (TCZ) could reduce mortality and/or morbidity in severe COVID-19.

Objectives: To determine whether baseline IL-6 serum levels can predict the need for IMV and the response to TCZ.

Methods: We performed a retrospective observational study including hospitalized patients diagnosed with COVID-19. Clinical information and laboratory findings, including IL-6 levels, were collected approximately 3 and 9 days after admission to be matched with pre-and post-administration of TCZ. Multivariable logistic and linear regression were used to analyze predictors of the need for IMV and evolution of the arterial oxygen tension/fraction of inspired oxygen ratio (PaO_2/FiO_2) respectively. Mortality was assessed through survival analysis and Cox proportional hazards modelling.

Results: 146 patients were studied, 66% were male with a median age of 63 years (table 1). 44 (30%) required IMV and 58 (40%) received TCZ, their main features are shown in tables 2 and 3 respectively. IL-6 levels showed a negative correlation with PaO_2/FiO_2 (r= -0.38; p < 0.001) and high levels (>30 pg/ml) discriminated patients requiring IMV with an AUC of 0.73. Furthermore, high IL-6 levels predicted the need for IMV [OR= 7.1 (95%CI 3.02 to 16.62)] (table 4) and early administration of TCZ (< 11 days from symptom onset) in these patients was associated with an improvement of the PaO_2/FiO_2 (p=0.048). Patients with high IL-6 and not treated with TCZ showed higher mortality [HR= 4.6 (1.7 to 12.7)], as well as those with low IL-6 treated with TCZ [HR= 3.6

(1.3 to 10.0)]. No serious adverse events were observed in the TCZ-treated group.

Table 1. Baseline clinical characteristics and laboratory findings of the study population

	Study Population (n = 146)
Age	63 (54-71)
Male sex	97 (66)
Comorbidities	100 (69)
Duration of symptoms at admission (days)	6 (4-7)
Baseline PaO2/FiO2	215 (112-310)
Treatment during hospitalization	
Hydroxychloroquine	137 (96)
Lopinavir/Ritonavir	119 (83)
Azithromycin	82 (57)
Interferon-β	7 (5)
Glucocorticoids	85 (59)
Methylprednisolone bolus	61 (42)
Laboratory Findings	
White Blood Count (10^3/mm^3)	7.64 (5.25–10.68)
Lymphocyte Count (10^3/mm^3)	0.83 (0.60–11.7)
Creatinine. mg/dl	0.86 (0.70-1.10)
LDH (U/L)	341 (256-461)
CK (U/L)	72 (48-155)
Serum IL-6 (pg/ml)	21.36 (7.53-54.21)
Ferritin (ng/ml)	1,598 (830-2,305)
CRP (mg/dL)	11.55 (5.16-22.53)
PCT (ng/ml)	0.15 (0.10-0.35)
D-dimer (mg/ml)	0.75 (0.48-1.48)

All categorical variables are expressed as number (%) and quantitative variables as median (p25-p75). PaO2/FiO2: arterial oxygen tension - fraction of inspired oxygen ratio; LDH: Lactate Dehydrogenase; IL-6: Interleukin-6; CRP: C-reactive protein; PCT: Procalcitonin.

Table 2. Baseline clinical characteristics of groups requiring vs not requiring Invasive Mechanical Ventilation

	Invasive Mechanical Ventilation		
	Required (n = 44)	Not-required (n = 102)	P value
Age	63.5 (56.5-72)	62 (54-71)	0.517
Male sex	32 (73)	65 (64)	0.291
Comorbidities	30 (68)	70 (69)	0.893
Duration of symptoms at admission (days)	5 (5-7)	7 (4-8)	0.265
Baseline PaO2/FiO2	125.5 (75-207)	247 (172-348)	< 0.001
Treatment during hospitalization			
Hydroxychloroquine	38 (86)	99 (100)	< 0.001
Lopinavir/Ritonavir	38 (86)	81 (82)	0.502
Azithromycin	24 (55)	58 (59)	0.652
Interferon-β	3 (7)	4 (4)	0.676

Glucocorticoids	27 (61)	58 (59)	0.755
Methylprednisolone bolus	21 (48)	40 (40)	0.414
Laboratory Findings			
White Blood Count (10^3/mm^3)	9.39 (6.59-13.31)	6.93 (5.13-8.78)	< 0.001
Lymphocyte Count (10^3/mm^3)	0.74 (0.58-1.08)	0.87 (0.62-1.26)	0.029
Creatinine (mg/dl)	0.99 (0.71-1.20)	0.85 (0.72-1.1)	0.398
LDH (U/L)	413 (315-496)	302 (224-443)	0.001
CK (U/L)	67 (39.50-167.50)	94 (59-140)	0.617
Serum IL-6 (pg/ml)	49.20 (17.28-103.57)	16.08 (6.09-42.03)	< 0.001
Ferritin (ng/ml)	1,665 (602-2,765)	1,573 (1,012-2,300)	0.832
CRP (mg/dL)	17.09 (7.69-28.98)	10.13 (4.83-18.48)	0.003
PCT (ng/ml)	0.29 (0.14-0.46)	0.13 (0.08-0.26)	0.001
D-dimer (mg/ml)	0.92 (0.56-2.31)	0.71 (0.48-1.19)	0.058

All categorical variables are expressed as number (%) and quantitative variables as median (p25-p75). PaO2/FiO2: arterial oxygen tension - fraction of inspired oxygen ratio; LDH: Lactate Dehydrogenase; IL-6: Interleukin-6; CRP: C-reactive protein; PCT: Procalcitonin.

Table 3. Baseline clinical characteristics of groups treated vs not treated with Tocilizumab

	Tocilizumab Treated (n = 58)	Not treated (n = 88)	P value
Age	61 (54-70)	64 (54-72)	0.288
Male sex	40 (69)	57 (65)	0.600
Comorbidities	35 (61)	64 (73)	0.124
Duration of symptoms at admission (days)	6 (5-7)	7 (4-8)	0.612
Baseline PaO2/FiO2	137 (88-232)	248 (183-348)	< 0.001
Treatment during hospitalization			
Hydroxychloroquine	53 (93)	84 (98)	0.171
Lopinavir/Ritonavir	51 (89)	68 (79)	0.103
Azithromycin	33 (58)	49 (57)	0.913
Interferon-β	2 (4)	5 (6)	0.532
Glucocorticoids	38 (67)	47 (55)	0.152
Methylprednisolone bolus	31 (54)	30 (35)	0.018
Laboratory Findings			
White Blood Count (10^3/mm^3)	7.99 (5.17-11.85)	7.52 (5.4-10.36)	0.527
Lymphocyte Count (10^3/mm^3)	0.74 (0.52-0.997)	0.93 (0.66-1.47)	0.001
Creatinine (mg/dl)	0.83 (0.70-1.05)	0.90 (0.72-1.14)	0.177
LDH (U/L)	425 (302-510)	293.5 (221-388)	< 0.001
CK (U/L)	69 (38-270)	75.5 (49-125)	0.785
Serum IL-6 (pg/ml)	41.85 (12.37-71.95)	16.25 (6.27-44.95)	0.007
Ferritin (ng/ml)	1,888 (1,152-2,844)	1,461 (471-1,861)	0.038
CRP (mg/dL)	13.73 (8.75-27.08)	9.09 (4.78-19.31)	0.005
PCT (ng/ml)	0.25 (0.13-0.36)	0.14 (0.1-0.3)	0.045
D-dimer (mg/ml)	0.75 (0.48-1.48)	0.71 (0.53-1.22)	0.491

All categorical variables are expressed as number (%) and quantitative variables as median (p25-p75). PaO2/FiO2: arterial oxygen tension - fraction of inspired oxygen ratio; LDH: Lactate Dehydrogenase; IL-6: Interleukin-6; CRP: C-reactive protein; PCT: Procalcitonin.

Table 4. Logistic regression model for invasive mechanical ventilation

	OR	p	95%CI
COPD	5.41	0.030	1.17 to 24.94
White Blood Count (10^3)	1.05	0.116	0.99 to 1.12
High baseline IL-6 levels*	7.09	< 0.001	3.02 to 16.62

OR: Odds Ratio; 95%CI: 95% Confidence Interval; COPD: Chronic Obstructive Pulmonary Disease; IL-6: interleukin 6. *High IL-6 was considered if >30 pg/ml.

Conclusions: High baseline IL-6 levels predicts IMV requirement in patients with COVID-19 as well as the response to treatment with TCZ. These findings can be of help in guiding clinicians for an early and adequate indication for IL-6 blockade.