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BLOOD IL-6 LEVELS AS A PREDICTOR OF THE CLINICAL COURSE SEVERITY IN COVID-19 INFECTION: DATA FROM THE REPUBLIC OF ARMENIA

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Abstract

Patients with severe cases of COVID-19 infection can develop acute respiratory distress syndrome, septic shock, multiple system organ failure, bleeding, and coagulation dysfunction. Severe forms of COVID-19 are characterized by viral pneumonia patterns and are frequently associated with elevated serum levels of pro-inflammatory cytokines forming a "cytokine storm". Among the mediators of cytokines release syndrome, interleukin-6 is one of the key cytokines. Tocilizumab, a monoclonal antibody against interleukin-6 receptor, may provide clinical benefit for selected COVID-19 patients with high inflammatory biomarkers. In this prospective study, we aimed to correlate the blood levels of interleukin 6, C-reactive protein, procalcitonin and other biomarkers to the clinical course and outcome of COVID-19 patients in our study cohort.

Our study shows that several biomarkers and in particular serum interleukin-6 levels differ according to disease severity in COVID-19 infection. Serum interleukin-6 levels were also significantly increased in non-survivors and could raise the potential benefit of tocilizumab for selected cases of COVID-19 infection. Data about the efficacy of tocilizumab are conflicting. However, our data about tocilizumab may suggest a potential benefit, and is in-line with previous data about the absence of significant risk of super-infection. The early short-term administration of methylprednisolone in a 250-500mg/daily dosage revealed good results with and without concurrent tocilizumab therapy.

Keywords: *tocilizumab, Interleukin-6, C-reactive protein, procalcitonin, infection, cute respiratory distress*

Introduction

Patients with severe cases of COVID-19 infection can develop acute respiratory distress syndrome, septic shock, multiple organ failure, bleeding, and coagulation dysfunction. **[***Chen N et al., 2020; Huang C et al.,* 2020**]** Severe forms of COVID-19 are characterized by viral pneumonia patterns and are frequently associated with elevated serum levels of proinflammatory cytokines forming a "cytokine storm" **[***Zhuang M et al., 2020*]. Severe cases can also be associated with co-infections of bacteria and fungi [*Dey S et al., 2020*]. Although, the pathogenesis of COVID-19 is still not adequately delineated, in humans, COVID-19 appears to mainly affect the cells in the airways lining the alveoli, binding to receptors and entering the cells [*Bastola A et al., 2020* ; *Huang C et al., 2020*]. According to case studies, the virus preferentially infects the lower respiratory tract. Patients initially develop fever, cough and myalgias, and can progress to shortness of breath and complications from pneumonia [*Huang C et al., 2020*].

Cytokines including Interleukin 1 beta (IL-1β)

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and Interleukin-6 (IL-6) prime neutrophils for activation by chemo-attractants and upregulate intercellular adhesion molecules on endothelial cells. The resulting neutrophil adhesion to the vasculature promotes neutrophil diapedesis and infiltration into the affected tissues-in COVID-19 infection, initially into lung parenchyma, but subsequently into other organs. Once neutrophils migrate to sites of tissue inflammation, they degranulate and release proinflammatory cytokines and chemokines, proteases, antiviral proteins and toxic oxygen radicals. In the myocardium, neutrophils play a prominent role in the development of myocarditis and cardiogenic shock [*Belkaid Y et al.,2005; Alhogbani T, 2016; Ruan Q et al., 2020*]. Neutrophils can trigger a cascade of events in arteries that promote plaque destabilisation/rupture and thrombosis [*Bangalore S et al., 2020; Huang C et al., 2020; Wang D et al., 2020; Zhou F et al., 2020*].

Thrombosis is a hallmark of severe COVID-19 infection. Neutrophils release serine protease neutrophil elastase that inhibits the tissue factor pathway inhibitor and leads to generation of thrombin, the most potent activator of platelets. Neutrophil extracellular traps provide a platform to activate coagulation via active neutrophil elastase adherent to extracellular neutrophil deoxyribonucleic acid. Activated neutrophils and other leukocytes also aggregate with platelets directly to further exacerbate inflammo-thrombosis. In the setting of extreme inflammatory states, activated neutrophils adhere directly to each other in a process known as leuko-aggregation, producing significant but usually transient vascular occlusions. Finally, neutrophils also contribute to thrombosis via cytokine-induced release of α-defensin from neutrophil granules.

Tocilizumab is a monoclonal antibody which inhibits interleukin-6- receptor. interleukin-6 is a key cytokine in inflammatory storm thought to result from increased alveolar-capillary blood-gas exchange dysfunction, impaired oxygen diffusion, and can eventually lead to pulmonary fibrosis and organ failure [*Yang X et al., 2020*]. Based on some reports, tocilizumab may be an effective drug to disrupt this pathway in COVID-19 patients. [*Hu B et al 2017; Sheppared M, 2017; Michot JM et al.,2020*]. Tocilizumab was previously approved by the Food and Drug Administration for the treatment of cytokine-release syndrome [*Sebba A, 2008*] and may provide clinical benefit for selected COVID–19 patients with high inflammatory biomarkers. Several recent randomized trials showed conflictual results about the benefit of tocilizumab, but the French CORIMMUNO and the English RECOVERY trials showed a significant benefit in overall mortality of tocilizumab, particularly when combined with steroids, in severe COVID-19 cases.

In this study, we aim to correlate the blood levels of IL-6, C-reactive protein (CRP), procalcitonin and other biomarkers to the clinical course and outcome of COVID-19 patients from our database at the "Nork" Infectious Diseases Clinical Hospital where most hospitalized COVID-19 patients are treated in the Republic of Armenia.

Material and Methods

The prospective clinical study was conducted over a 6-month period from July – December 2020, at the "Nork" Infectious Diseases Clinical Hospital in Armenia. All consecutive patients with COVID-19 infection were included. The diagnosis of COVID-19 was made as recommended by positive Polymerase chain reaction (PCR) and/or suggestive computed tomography (CT) in the absence of other etiology. Serum IL-6 levels were tested in all patients. Data about clinical, radiological features and blood levels of lymphocytes, procalcitonin, ferritin, C-reactive prot and other laboratory data were recorded at baseline.

Per hospital protocol and recommendations of Boston Medical Center [*Vu C et al.,2020*], tocilizumab was administered to patients with the following criteria: ≥10 liters of nasal cannula oxygen to maintain a Saturation of hemoglobin as measured by pulse oxim-

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

etry (SPO2) > 93%, signs of clinical deterioration, at least two increased inflammatory markers (IL-6 > 70 *pg/ml*, C-reactive protein > 100 *mg/L*, ferritin> 1000 *ng/mL*, D-dimer > 1*mcg/ml*). Tocilizumab was not recommended for patients with concomitant bacterial infections, baseline alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 times the upper limit of normal (ULN), baseline platelet count $< 100 \times 10^9/L$, baseline absolute neutrophil count $< 1.5 \times 10^9/L$. tocilizumab was used at 8*mg/kg* (up to 800 *mg* total) intravenously. Per protocol, doses were given once or divided in two doses 12 hours apart; and administered alone or in combination with corticosteroids. If no clinical improvement in the signs and symptoms of cytokine release syndrome occurred after the initial dose, it was administered up to 3 additional doses.

Ethics and approval: This study was approved by the Internal Review Board of the "Nork" Infectious Diseases Clinical Hospital. Records were anonymized to protect identifying patient information.

Statistical analysis: Data are expressed as means with SD or medians with ranges and numbers with frequencies. To compare quantitative data the chi-square tests or ANOVA were used, and for qualitative data the Fischer's exact test. The p value less than 0.05 was considered as statistically significant. All statistical analysis were conducted using GraphPad software, version 6.5.

Results

Characteristics of COVID-19 infected patients: One hundred two patients with COVID-19 infection were included in the study with a median age 54.9 years (26-84), and 47% male. Patients' general characteristics are in Table 1. Tocilizumab was used in combination with steroids in 16 cases. On admission, COVID-19 pneumonia was confirmed in 89 cases (87%), the lowest oxygen saturation on admission was 35% on room air. During hospitalization, 29 cases (28%) were hospitalized in the intensive care unit. Mortality in this cohort was 10.8% (Table 1).

Computerized tomography (CT): Patients were classified as moderate (n=20), severe (n=52) and critically-ill (n=30) COVID-19 infection (Table 2). In the moderate severity group, 67% were female, with a mean age of 49±22, of which 16 had comorbidities: hypertension (9), diabetes (6), obesity (5), heart ischemic disease (3), rheumatoid arthritis (1). In this group there were no patients treated with tocilizumab and no deaths.

In the severe disease COVID-19 patient group, the mean age was 56 years (26-79) with 41% males, 88.4% had comorbidities. Hypertension was recorded in 29 cases, diabetes type 2 in 17 cases, Body mass index (BMI) <30 in 38 cases,

Table 1.

Baseline characteristics and outcomes of COVID-19 patients.

Patient characteristics	N = 102
Demographics	
Age, (years)	55.2 ± 29.1
Sex, male (n;%)	48 (47%)
Comorbidities :	
• None	13 (12.7%)
• One	37 (36.3%)
• Two	31 (30.4%)
• More than two	20 (19.6%)
Baseline features (on admission)	
Duration of symptoms before admission, days	8.9 ± 5.8
Oxygen saturation %	64.8± 30.6
Respiratory rate, per min,	29.6 ± 9.8
Heart rate, per min,	118.3±45.8
CT scan performed	89 (87.3%)
Lung involvement on CT scan, median with quartiles	25-95 % (<25%- >70%)
Lung involvement on CT-scan >50%	49 (48%)
Do not resuscitate status	13 (12.7%)
Treatment regimens	
Dexamethasone	68 (66.7%)
Methylprednisolone	11 (10.7%)
Tocilizumab + steroid combination	16 (15.6%)
Outcomes at the end of the follow-up	
Intensive care unit admission	29 (28.4%)
Invasive mechanical ventilation	3 (2.9%)
Non-invasive CPAP	12 (11.8%)
Death	11(10.8%)
Hospitalisation duration, days,	18.1 ± 14.4

Table 2.
Correlation in inflammatory marker levels and the clinical course severity in COVID-19 patients

	Moderate N=20	Severe N=52	Critically-ill N=27	P
Age (years)	49.4±22.3	56.2±24.6	58.5±26.2	0.0028
C-reactive protein (*mg/L*)	46.6±38.5	121.8±89.6	284.7±155.6	<0.0001
Ferritin (*ng/ml*)	356±295	2207±1523	2940±1836	<0.0001
Procalcitonin (*ng/m*)*l*,	0.03±0.08	0.13±0.12	0.24±2.9	0.02
Lymphocyte count (*x* 10^9*/L*)	1.3±0.8	0.9±0.47	0.83±0.54	0.0031
D-dimer (*FEU/ml*)	0.45±0.38	2.3±2.4	3.8±2.6	0.1
Interleukin 6 (*pg/ml*)	12.3±8.6	58.1±34.6	70.1±98.4	<0.0001
Hospitalization duration, (*days*)	5.3±2.2	13.6±7.7	16.5±8.4	<0.0001
Deaths n (*%*)	0	5 (9.6)	6 (20)	0.03*

*critically-ill versus moderate COVID-19

heart ischemic disease in 9 cases, chronic heart failure in 9 cases, chronic kidney disease in 2 and one case of systemic scleroderma, respectively. All patients had hypoxia. SpO2 levels 80% [71-89%] on room air were treated with corticosteroids, and received oxygen therapy with nasal cannula or oxygen mask, 5 patients were admitted to the intensive care unit and 2 of them were treated with Continuous Positive Airway Pressure (CPAP), without the need for invasive ventilation. In this group, 5 patients were treated with tocilizumab, of which 4 made a complete recovery. One patient died of pulmonary embolism.

In the critically-ill COVID-19 patients, the mean age was 58 years (31-78) and 27 of them with one or more of the following comorbidities: diabetes, hypertension, acute and chronic heart failure, arrhythmia, mental health disorders, rheumatic diseases, hypothyroidism. Nineteen of these patients were admitted to hospital with severe hypoxia SpO2 72-85% on room air. Disease progressed to critically severe during hospitalization and of them, 11 patients were transferred to the intensive care unit.

In this group, 10 patients received CPAP oxygen therapy, and three were intubated. Out of six patients received tocilizumab, a single dose was given to five, two doses to one patient, respectively. In three patients, recovery was recorded.

Interleukin-6 levels correlates with severity of COVID-19 infection: Comparing these three groups, the blood levels of CRP, procalcitonin and ferritin significantly increased with the disease severity (Table 3). Comparing these 3 severity groups, IL-6 levels significantly increased and were more elevated in critically-ill patients ($p < 0.05$). Critically-ill COVID-19 patients had a significantly higher mortality rate in comparison to the moderate and severe patients (Table 3, Fig. 1).

Interleukin-6 levels in survivors and non-survivors: IL-6, CRP and procalcitonin blood levels were significantly increased in non-survivors, whereas lymphocytes were significantly decreased (Table 2). Whereas age and associated comorbidities were not significantly different in survivors and non-survivors, lung involvement on CT-scan 75-90% was more frequent in non- survivors (Table 3).

Tocilizumab efficacy and safety: In our cohort, tocilizumab was administered in 11 cases, at dosage of 8*mg/kg*. Of them, a daily cumulative dosage was divided two times per 12 hour in five cases, and 400*mg* was administered to four cases and 600*mg* to two cases in one injection, respectively. In those patients treated with divided tocili-

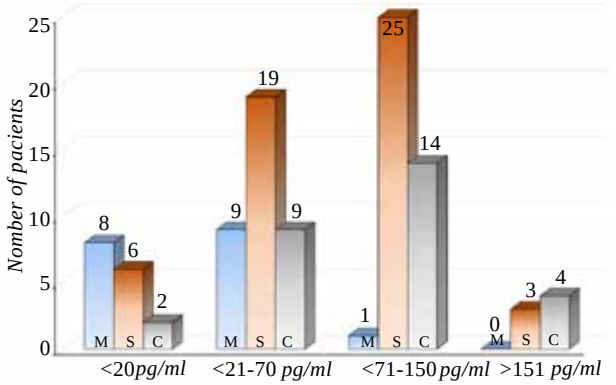

Figure 1. *Correlation in Interleukin-6 level and the clinical course severity. Notes: Groups of pacients (M) - moderate, (S) - severe and (C) critically ill.*

Table 3.

Characteristics of laboratory examination bio-parameters and lung involvement in survivors and non-survivors

Characteristics	Survivors n=91	Non-survivors n=11	P
Interleukin 6 (*pg/ml*)	115.7±106.4	122.7±133.1	0.014
C-reactive protein (*mg/L*)	164.3±128.1	241.3±167.8	<0.001
Ferritin (*pg/ml*)	1.89±1.86	2.49±2.40	0.07
Procalcitonin (*ng/ml*)	1.92±1.9	4.53±4.48	0.009
Lymphocyte count (*x 10^9/L*)	0.92±0.55	0.52±0.38	<0.001
D-dimer (*FEU/ml*)	8.3±7.9	10.2±9.8	0.1
Obesity	42 (44.2%)	8 (72.7%)	0.1
Diabetes melitus	38 (40%)	7 (63.6%)	0.3
Heart diseases	58 (61.1%)	9 (81.8%)	0.3
Lung involvement on CT -scan			
< 25 %	12 (12.6%)	0	0.5
25 - 50 %	23 (24.2%)	1 (9.1%)	0.3
50-75 %	39 (40%)	2 (18.2%)	0.6
75-90%	17 (17.8%)	6 (54.5%)	0.03
> 90 %	3 (3.2%)	4 (36.3%)	0.0006
Hospitalisation duration, (*days*)	13.2 ±8.7	11.6± 10.9	

Table 4.

Adverse events in patients receiving tocilizumab

Adverse events	Total N=102	Group 1 N=20	Group 2 N=52	Group 3 N=30
Acute respiratory distress syndrome	58 (51.96%)	0	33 (61.5%)	25 (70%)
Acute myocardial infarction(n;%)	2 (1.96%)	0	1 (1.9%)	1 (1.9%)
Heart failure	5 (4.9%)	0	2 (3.8%)	3 (10%)
Arrhythmia	27 (26.47%)	8 (40%)	15 (28.8%)	4 (13.33%)
Sepsis	3 (2.9%)	0	1 (1.9%)	2 (6.67%)
Encephalopathy	7 (6.9%)	0	4 (7.7%)	3 (10%)
Uveitis	1 (0.98%)	1 (5%)	0	0
Elevation of ALT, AST	9 (8.8%)	2 (10%)	6 (11.5%)	1 (3.33%)
Nasal bleeding	13 (12.7%)	2 (10%)	7 (13.5%)	4 (13.33%)

zumab dosage the decrease of CRP level was recorded on the 2nd and 3rd day following injection, in the others who received a daily cumulative dosage in one injection on the 3rd -4th day, respectively. Comparing six patients with critically ill COVID-19, who received tocilizumab to those who did not receive tocilizumab, three patients died in tocilizumab-administered vs. three ones in no tocilizumab-administered group, respectively. The mean hospitalization in patients administered tocilizumab was 17.8 days (15-24) vs. 16.9 days in untreated ones. Steroid therapy was combined with tocilizumab in all patients. Tocilizumab was combined with steroid therapy on 5-15th day. Recovery was recorded the 4th day after starting tocilizumab injection, and on the 10-12th day of steroid therapy.

There were no deaths attributed to bacterial origin in patients who received tocilizumab-A moderate elevation of alanine transaminase and aspartate transaminase was noted in 2 cases (Table 4).

Discussion

Limitations: The study was a prospective study with a small cohort of 100 patients.

Our study shows that several biomarkers and in particular IL-6 blood levels differ according to the disease severity in COVID-19 infection. IL-6 blood levels were also significantly increased in non-survivors and could raise the potential benefit of tocilizumab for selected cases of COVID-19 infection. Our data about tocilizumab could suggest a potential benefit and are in line with previous data about the absence of significant risk of infection.

Previous data showed an increased IL-6 levels in COVID-19 patients. A total of nine studies with laboratory-confirmed 1426 patients (mean age: 53.0 ± 6.4 years, females: 46.6%) were included. All studies originated from China, and study duration ranged from 1 January to 28 February 2020. A

comparison of mean serum IL-6 for severe COVID-19 and non-severe COVID-19 was performed in seven studies. The mean serum IL-6 was 56.8 (41.4±72.3 *pg/mL*) and 17.3 *pg/mL* (13.5±21.1 *pg/mL*) for severe and non-severe COVID-19 group, respectively. This was statistically significant (MD: 38.6 *pg/mL*, 95% CI: 24.3±52.9 *pg/mL*; $P < .001$, $I^2 = 98.5\%$. A total of five studies reported data on overall mortality and serum IL-6 in COVID-19 patients. The pooled prevalence of mortality across these studies was 2.9% (95% CI: 1.8%±4.0%). Meta-regression demonstrated that increasing mean IL-6 on admission was associated with an increased likelihood of mortality (Q: 0.01, 95% CI: 0.01±0.03; $P = 0.03$). **[***Aziz M et al.,2020* **]**

Data about the efficacy of tocilizumab are conflicting, but recent data from French and English CORIMMUNO and RECOVERY trials showed promising results. RECOVERY showed in particular the benefit of the combination of steroids to tocilizumab, as it was used also in our cohort. Indeed, all tocilizumab treated patients also received steroids, dexamethasone (DEXA) or methylprednisolone.

The best strategy, in particular the time to tocilizumab and potential re-treatment based on IL-6 levels should be better assessed in prospective trials. Safety is a particularly challenging question in patients with viral infection. Our data are similar to previous reports and show no increased risk of bacterial and fungi infection induced by the use of short-term tocilizumab and steroids in COVID-19 patients.

These data support the general anti-inflammatory effect of tocilizumab in combination with corticosteroid therapy that have a promising outcome. In terms of early administration of tocilizumab, it showed higher effect in improving the clinical manifestations and inflammatory marker regulation in lower cumulative dosage of steroids. The early and short-term administration of methylprednisolone in a 250-500*mg/daily* dosage revealed good results with and without combination with tocilizumab.

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