

Tocilizumab in Covid-19 Interstitial Pneumonia: A Phase II Pilot Study

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Abstract

Background: Multiple studies have been conducted to investigate Tocilizumab in patients with cCOVID-19 pneumonitis. However, published reports show conflicting results, largely due to weak retrospective designs and heterogeneity in critical methodological issues.

Methods: This open-label trial was structured according to the Simon's optimal two-stage design in order to clarify which patients could really benefit from anti-IL6 strategies and how a future randomized trial should be designed to provide reliable and unequivocal results. 46 patients received a single infusion of Tocilizumab. Inclusion criteria were: SARS-CoV2 infection diagnosed by rt-PCR, multifocal interstitial pneumonia, need of oxygen therapy (FiO2 50%) to maintain SO2 >93%, recent (within the last 24 hours) worsening of lung function. Clinical outcomes were established a priori to assess whether a patient responded to treatment. A low number of carefully chosen clinical and biological markers was measured in order to test their predictive values. Primary end point was early and sustained clinical response.

Results: Twenty-one (46%) patients fulfilled pre-defined response criteria. Lower levels of IL-6 at 24 hours after tocilizumab infusion ($p=0.049$) and higher baseline values of PaO2/FiO2 ($p=0.008$) predicted a favorable clinical response. Patients not improving at 72 hours were also non-responder at day 7. 11/25 of non-responder patients were intubated and 7 died. High levels of vWF were detected in all sera, with a tendency towards higher concentrations in the non-responder group.

Conclusions: Objective clinical response rate overcame the pre-defined threshold of 30%. Efficacy of tocilizumab to improve respiratory function in selected patients with severe COVID-19 pneumonitis warrants investigations in randomized trials.

Trial registration: NCT 04315480

Introduction

Multifocal interstitial pneumonia represents the most common cause of admission in intensive care units (ICU) and death during SARS-CoV2 infection. Available data, mostly collected on other coronavirus infections with similar clinical behaviour, highlight an intense "cytokine storm" with a consequent inflammatory infiltrate of pulmonary interstitium, macrophage activation, giant cells formation and subsequent extended alveolar damage^{[i],[ii],[iii]}.

Tocilizumab, an anti-IL-6 receptor monoclonal antibody, has proved effective in rheumatoid arthritis, as well as in diseases characterized by an intense systemic inflammatory activation^{[iv],[v]}. Moreover, small case series from China and Italy suggest that IL-6 blockade induces rapid clinical improvement in patients affected by COVID-19 interstitial pneumonia^{[vi],[vii],[viii],[ix]}.

However, conflicting results have been recently reported, in particular in patients affected by more severe disease. Indeed, favorable effect of the drug on mortality and risk of intubation^[x] has not been confirmed

in other studies[xi].[xii].

Weak retrospective designs, together with heterogeneity in enrolled population characteristics and outcome definition and measurement hamper a reliable clinical data interpretation.

To investigate which patients with severe and worsening pneumonia could benefit of a single intravenous infusion of Tocilizumab, we designed a multicentre, prospective, open-label trial, structured according to the 'Simon's optimal two-stage design' with the goals:

1. to confirm that a significant proportion of patients can obtain a rapid and relevant improvement of respiratory function;
2. to explore clinical and serological parameters useful to predict clinical response;
3. to acquire elements useful to design future unequivocal randomized trials

Methods

Study Design

On March 12th, 2020 the Internal Ethical Board of Ospedali Riuniti-Ancona (Italy) authorized off-label treatment of patients affected by SARS-CoV2 related severe interstitial pneumonia with tocilizumab.

The study was structured according to Simon's optimal two-stage design^[1]. Fourteen patients (variable: n_1) entered the first stage of the trial. Enrollment would have been stopped and the drug rejected if $<10\%$ of the patients (variable: P_0) had met the primary end point 72 hours after the administration of tocilizumab. Conversely, the study would have been continued until at least 46 patients were enrolled in total (variable: n). The drug would have been rejected in the case of a positive response rate $<30\%$ (variable: P_1) of the patients completing the study.

The values of variables n_1 , n , P_0 , and P_1 were set to obtain a probability ≤ 0.01 of accepting a drug worse than P_0 after the first stage and a probability ≤ 0.2 of rejecting a drug better than P_1 at the end of the study.

Study Population

Between March 12th and March 26th, 46 consecutive patients were treated.

Inclusion criteria were: patients 18 to 90 years of age; SARS-CoV2 Infection diagnosed by rt-PCR, multifocal interstitial pneumonia confirmed by Rx or chest CT-scan, need of oxygen therapy (FiO2 50%) to maintain peripheral oxygen saturation (SO2) $>93\%$, recent (within the last 24 hours) worsening of lung function, defined as a decrease of SO2 $>3\%$ points and/or decrease of the ratio of PaO2 to FiO2 (P/F) $>50\%$ and/or P/F below 150 mm/Hg.

Exclusion criteria were: severe heart failure, active bacterial infection, hematological malignancy, neutrophil count $< \times 10^9/L$, platelet count $< 50 \times 10^9/L$, Alanine Aminotransferase (ALT) 5-fold above the upper normal level (UNL), inability to give a valid informed consent.

Drug administration

Tocilizumab was administered as a single infusion of 8mg/Kg (max 800mg), after a premedication with 40 mg of 6-Methylprednisolone. Written informed consent was obtained before the infusion.

Concomitant therapies were allowed according to local protocols. No patient received systemic corticosteroids. All patients were on oxygen therapy, administered either by Ventimask (V) or C-PAP.

Assessment

Complete clinical evaluation, assessment of SO_2 , arterial blood gas analysis (when possible), recording of both FiO_2 and type of ventilation were performed at baseline, and after tocilizumab infusion at 24 and 72 hours and day 7. Complete blood count, ALT, D-dimer, and creatinine. were also performed at the same time points.

CT-Scan

High Resolution chest CT- scan (HRCT) was performed at baseline in 33 cases and at day +7 in 21 patients.

Two independent Pulmonologists, with 10 and 12 years of experience, evaluated the images blinded for sequence and final decisions was reached by consensus.

Assessment of radiological pattern, and definition of the extent of parenchymal involvement were performed and scored as described [ii] [iii].

The extent of parenchymal involvement at HRCT was first scored by visually evaluating the percentage of lesions' involvement at lobar basis according to a 5-point categorical scale. A Total Severity Score (TSS; range from 0 to 20) was obtained by summing the scores of the five lobes.

Assays

Serum levels of IL-6 (Immulite 2000, Siemens), von Willenbrand Factor (vWF) (Thermo Scientific), Surfactant protein D (SP-D) (BioVendor) and Thrombomodulin (ABCAM) were determined with commercially available enzyme-linked immunosorbent assay following the manufacturers' recommendations.

Response criteria

The primary outcome was the rate of responder patients. A patient was *a-priori* defined as responder if fulfilling either criteria 1 or 2 AND criteria 3 of the ones listed below:

1. Improvement of oxygen saturation by more than 3% points and/or increase in P/F by 50% and/or increase P/F above 150 mmHg 72 hours after tocilizumab AND persistence of this improvement at day 7;
2. No worsening of respiratory function as defined in the inclusion criteria at 72 hours AND improvement of oxygen saturation by more than 3% points and/or increase in P/F>50% and/or increase P/F above 150 mmHg at day 7;
3. No need of endotracheal ventilation for all or CP for those not requiring it at baseline

Secondary outcomes were: 1. rate of admission to intensive care unit for endotracheal intubation or evidence of multiple organ dysfunction; 2. death; 3. rate of severe drug-related adverse events.

Adverse Events

Patients were examined every day until discharge and all possible adverse events were recorded. Adverse events were classified according to U.S. Department of Health And Human Services criteria ^[iv].

Statistical analysis

Data were expressed as median (and range or Interquartile range) unless otherwise stated. Comparisons were made using Mann-Whitney U-test or chi-square test as appropriate. Two multivariate logistic regression analyses were performed using the primary outcome as dependent binary variable and the possible prognostic factors as independent variables. As possible prognostic variables we considered age, sex, number of comorbidities, PaO₂/FiO₂ at baseline, heparin and HYQ as co-treatments, and either IL-6 at baseline or IL-6 at 24h. A significance level alpha=0.05 will be used for all the statistical analyses.

Results

Characteristics of Patients

Since five out of the first 14 patients met the primary outcome, enrollment was completed up to a total of 46 cases. Demographic and clinical characteristics are summarized in Table 1. Median age was 67.5 (range 34-89) years and median disease duration before the drug infusion was 9.5 (range 2-21) days. Thirty-three patients (72%) were male and 13 (28%) were female; all Caucasian.

All patients were non-smokers, frequently affected by hypertension (63%). Five (11%) patients were affected by type II diabetes, 3 (7%) by renal failure, 2 (4%) by chronic heart failure. About half of observed patients had no co-morbidities at the time of enrolling.

All the subjects were affected by pneumonitis requiring high-flow oxygen therapy. Twenty-five (63%) patients had severe respiratory failure, characterized by a P/F ratio <150 mmHg and 30 (65%) were on C-

PAP.

HRCT, available in 33 (72%) patients, revealed a diffuse pulmonary involvement and 23 (69%) had a TSS of 8 or more, typical of the most severe patterns¹².

Forty-one (89%) patients were on Hydroxychloroquine (HYQ; 600mg/d), 35 (78%) on antivirals and 30 (67%) on antibiotics. Only 18 (39%) received prophylactic doses of Low Molecular Weight Heparin.

Laboratory tests performed at baseline showed a moderate increase of D-dimer, lymphocytopenia and a slight elevation of ALT.

Ground glass opacities (14/33, 42%) and consolidations only (11/33, 33%) were the most prevalent CT-scan patterns.

Treatment Response

According to the *a priori* criteria, 72 hours after tocilizumab 20 (43.5%) patients had an objective improvement and maintained the improvement in lung function at day 7. In 14 patients improvement was already apparent 24 hours after drug administration. One further patient was stable after 72 hours and improved at day 7. Overall, 21 (45.6%) of the enrolled patients could be classified as responder. None underwent endotracheal intubation, admission to ICU or died.

In this subgroup, the median P/F significantly increased at 72 hours compared to baseline value (median; IQ range: 250;197-362 vs 163;136-241, $p=0.009$).

At day 7, twenty-five patients were non-responder, although three of them had shown a transient improvement after 72 hours. Eleven (44%) of 25 were intubated a median of 2 (range 0-9) days after treatment and 4 died. Of the remaining 14 patients, 3 died and 11 were still classified as non-responder.

All responder patients were discharged after a median of 21 days (IQ range 17-27) after tocilizumab infusion, compared to 25.5 days (IQ range 20-34.25) of the sixteen non-responder patients. Two patients are still intubated 60 days after treatment.

Patients with P/F >150 mmHg at baseline ($P=0.003$) and lower CT-scan TSS ($p=0.008$) were most likely to benefit from tocilizumab (Table 2).

Higher levels of IL-6 at baseline correlated with poor response ($p=0.02$). At 24 and 72 hours, an evident increase in IL-6 serum levels were observed both in responder and in non-responder subjects. However, the increase of IL-6 serum levels was clearly greater in non-responders (Fig 1 and Table 4).

No significant differences emerged between responder and non-responder groups regarding age distribution, sex, number of comorbidities, concomitant therapy with HYQ or LMWH and baseline levels of lymphocytes or D-dimer (Table 2).

No differences regarding to different CT-scan patterns emerged from the comparison between responders and non-responders.

We could compare chest CT-scan taken at baseline and after 7 days in 21/46 patients (13 responder and 8 non-responder). Changes in CT-scan poorly correlate with clinical course. In particular, 3/13 (23%) of responders and 2/8 (25%) of non-responders underwent a substantial improvement, while in 1/13 (7,7%) and 2/8 (25%) of non-responders a significant worsening was evident. In the remaining cases, CT-scan longitudinal evaluation documented only minor changes.

Markers of endothelial and alveolar damage

Increased levels of vWF were detected in sera at baseline and 72 hours after drug infusion, particularly in non-responder group. Thrombomodulin levels remained stable within the normal limits at baseline and after tocilizumab, in both groups.

The serum levels of SP-D, a glycoprotein secreted by type II pneumocytes and a potential surrogate marker of alveolar damage, were elevated at baseline in 35% of patients and the concentrations rose overtime, particularly in non-responder patients (Fig 1 and Table 4).

Multivariate analysis

In a multivariable model, lower IL-6 levels measured at 24 hours ($p=0.049$), and higher baseline values of P/F ($p=0.008$) were associated with better response to the drug (Table 3). In the alternative model, IL-6 levels at baseline did not emerge as independent variable.

Safety

Adverse events were reported in 29 (63%) of patients (Table S1). The most common was an increase in aminotransferases. Four patients reported a 3-fold ALT elevation from baseline and 10 patients a 5-fold increase at day 7. All these patients showed a normalization of liver enzymes within 14 days. No case of hepatic failure was observed.

In three patients (one responder and two non-responders) significant neutropenia ($<1 \times 10^9/L$) appeared more than 7 days after drug infusion. Two patients (one still neutropenic) were discharged without overt bacterial infections. The third patient was a non-responder and had a severe infection caused by *Corynebacterium Jeikeium* and *Clostridium difficile* one month after tocilizumab infusion and despite normal neutrophil count.

Six bacterial infections were reported in 6 patients, all after admission to the ICU. The relationship with the experimental drug was considered uncertain by the investigators.

Three patients, on hydroxychloroquine and lopinavir-ritonavir combination, suffered clinically relevant arrhythmias. One patient, had a new episode of atrial fibrillation (AF) soon after tocilizumab infusion,

with a spontaneous return to normal sinus rhythm within 24 hours. A second patient developed AF 24 hours after tocilizumab, and since this occurred with the worsening of respiratory function he was transferred to the ICU and intubated. The third patient developed AF within 24 hours after infusion and underwent successful pharmacological cardioversion.

After the detection of pulmonary embolism nine days after tocilizumab, one non-responder patient was anticoagulated and was discharged home once clinically improved.

Finally, in one hypertensive 77-year-old man a transient worsening of moderate-severe renal failure was observed.

No reaction has been reported during or after parenteral administration of tocilizumab.

Discussion

The present study shows that 7 days after a single dose of tocilizumab, 21 patients with severe pneumonia fulfilled the responder criteria and none required admission to ICU or died. These patients were part of the 23 patients subgroup who had improved at 72 hours. The responder rate (46%) overcame the predefined threshold of 30%, and thus the results justify future phase III randomized trials.

All 23 patients who did not improve at 72 hours were also non-responder at day 7. All the patients who died were in the non-responder subgroup.

These data indicate that the response obtained 24-72 hours after the administration of tocilizumab to patients with severe pneumonia foreshadows the likely prognosis.

At variance with what reported by others^[i], high baseline values of IL-6 did not predict the clinical outcome of our patients, rather more informative were the serum levels at 24 hours which better reflected the actual generation of IL-6 and thus the severity of the inflammation, as previously described in chronic inflammatory diseases^[ii]. The greater increase of the cytokine serum levels in patients who did not respond to tocilizumab support the hypothesis that IL-6 plays a major role in the pathogenesis of organ damage in this infection, as also reported by others^{[iii],[iv],[v],[vi]}.

While the increasing levels of SP-D accurately illustrate the on-going lung damage, vWF and thrombomodulin performed differently, the former higher in more severely affected patients at 72 hours, the latter stable and within the normal limits at all time points. Since vWF is produced constitutively in **endothelium**, while thrombomodulin is an **integral membrane protein** expressed on the surface of endothelial cells, our findings suggest that at least an abnormal breakdown of vWF may be involved in the microvascular damage in Covid-19 patients.

Thus, the conclusions that can be drawn from these set of data are: i. a significant portion of severely ill and deteriorating patients responded quickly to tocilizumab infusion; ii. Lower levels of IL-6, particularly 24h after drug infusion, higher P/F ratio and less extensive CT manifestations correlated with a better

response; iii. patients not improving after 24-72 hours, as well as those with unfavorable prognostic factors, should either receive a second administration of tocilizumab, as it has been proposed for patients with the cytokine release syndrome following the chimeric antigen receptor (CAR) T cell therapy[vii] or switched to other treatment regimen

Several adverse events occurred in our patients, not unexpectedly given the severity of the clinical conditions at baseline. Bacterial infections could be ascribed to the risk factors associated to the prolonged hospital stay or the viral infection itself, which rendered them susceptible to infections. The three episodes of AF, which occurred within 24 hours from tocilizumab, seem to point to a direct relationship with the medication. However, it is difficult to consider tocilizumab the sole culprit since: i. arrhythmias are frequent in COVID-19 patients[viii]; ii. Tocilizumab seems to reduce the incidence of disorders of cardiac rhythm and cardiac events in inflammatory diseases[ix],[x]; iii all three patients' co-treatments could have, at least, contributed to the rhythm abnormalities.

The most relevant elements of our prospective study are the following: i. treatment of a homogeneous population of patients; ii. enrollment of patients with severe disease manifestations and poor prognosis; iii. pre-specified clinically relevant outcomes; iv. sample size determined to provide the power required by the Simon's optimal two-stage design.

Our study has, however, some weaknesses. First, it was a small, open-label trial without a control group. It cannot be ruled out that the improvement observed in some patients was due to a milder disease. However, in our opinion, the enrollment of patients with severe pneumonia and recent worsening of lung function in the previous 24 hours, and appraising as responder only those who rapidly ameliorated after treatment, mitigated this problem. Second, due to the frantic days of the pandemic, there was quite a number of missing data, albeit equally distributed between the responder and non-responder subgroups. Complete reports were, however, available from two-thirds of the enrolled patients. Third, the small study group makes the multivariate analysis exposed to the risk of "random effects", thus, the data should be compared with those of on-going prospective studies.

Conclusion

A single infusion of 8mg/Kg of tocilizumab appears a promising strategy to rapidly improve respiratory function in patients with severe and rapidly worsening COVID-19 lung disease, particularly with a P/F ratio >150mm/hg and lower generation of IL-6.

ClinicalTrials.gov: NCT 04315480

List Of Abbreviations

AF, atrial fibrillation

ALT, Alanine Aminotransferase

CP, CPAP

HRCT, High Resolution chest CT- scan

HYQ, Hydroxychloroquine

ICU, intensive care units

IL-6, interleukin 6

LMWH, Low Molecular Weight Heparin

P/F, ratio of PaO₂ to FiO₂

SO₂, oxygen saturation

SP-D, Surfactant protein D

TCZ, tocilizumab

TSS, Total Severity Score

UNL, upper normal level

V, Ventimask

vWF, von Willebrand antigen

Declarations

Ethics approval and consent to participate

The study was authorized on March 12th, 2020 by the Internal Ethical Board of Ospedali Riuniti-Ancona (Italy).

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

AG, GP and AF contribute in study design, acquisition and interpretation of data and were major contributors in writing the manuscript. MR contribute to statistical analysis of data. MM, SS and MP perform biological a laboratoristical analysis. All authors read and approved the final manuscript.

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Tables

Table 1. Demographic, clinical, laboratory and radiological characteristics of patients enrolled in the experimental.

	Patients
Number	46
Median age (range) -years	67,5 (34-89)
Sex (%)	
M	33 (72)
F	13 (28)
Comorbidities (%)	
Chronic heart failure	2 (4)
Hypertension	29 (63)
Diabetes	5 (11)
BPCO	0 (0)
Renal failure	1 (2)
Renal failure with renal transplatation	2 (4)
No comorbidity	21 (46)
1 comorbidity	17 (37)
2 comorbidities	6 (13)
2+ comorbidities	2 (4)
Smoke (%)	
actual	0 (0)
Former	4 (10)
na	4 (9)
Time between onset of symptoms and TCZ infusion	
days median (range)	9,5 (2-21)
na (%)	4 (9)
Time between onset of symptoms to hospital admission	
days, median (range)	7 (0-14)
na (%)	4 (9)
Respiratory function (baseline)	
Ventimask (%)	16 (35)

C-PAP (%)	30 (65)
P/F ratio >150 (%)	15 (37,5)
P/F ratio <150 (%)	25 (62,5)
na (%)	6 (13)
Concomitant Therapies (baseline) (%)	
Lopinavir-ritonavir or darunavir-cobicistat	35 (78)
Hydroxychloroquine	41 (89)
Antibiotics	30 (67)
Prophylactic LMWH	18 (39)
Laboratory features	
IL-6 pg/ml	45,15
median (25-75 IQ range)	(16,25-64,77)
na (%)	10 (22)
D-dimer ng/ml	387
median (25-75IQ range)	(300,5-600,5)
na (%)	11 (24)
Lymphocyte x10⁹/L	0,635
median (25-75IQ range)	(522,5-790)
na (%)	4 (9)
ALT U/l	30 (12-158)
median (25-75IQ range)	
na (%)	1 (2)
Extension of pulmonary involvement (Chest CT-scan Total Severity Score)	10
median (25-75 IQ range)	(7-12)
na (%)	13

na=not available

Table 2. Clinical, biological and radiological characteristics of responder and non-responder patients.

	Responders	Non-Responders	P-value[#]
Number (%)	21 (46)	25 (54)	
Age median (range)	68 (37-89)	65 (34-89)	ns
Sex			
M	15 (45)	18 (55)	ns
F	6 (46)	7 (54)	
Number of comorbidities			
0	11 (52)	10 (48)	ns
1	9 (53)	8 (47)	
2 or 2+	1 (13)	7 (88)	
PaO2/FiO2 at baseline			
>150 mm/Hg	12	3	χ^2 (df1,N 40)= 8,64 p=0,003
<150 mm/Hg	8	17	
mm/Hg median (IQ range; na)	163 (133-241; 1)	102 (88-142; 5)	
PaO2/FiO2 at 24h	211 (140-352; 5)	153 (121-177; 9) ^o	nap
median (IQ range; na)			
PaO2/FiO2 at 72h	250 (197-362; 6)	138 (77-179; 9) ^o	
median (IQ range; na)			
D-dimer ng/ml at baseline	379	445,5	ns
median (IQ range)	(274,5-480)	(344,25-618)	
Lymphocyte x10⁹/L at baseline	0,680	0,595	ns
median (IQ range)	(0,565-0,812)	(0,507-0,730)	
Prophylactic LMWH	6	13	ns
HYQ	18	23	ns
Extension of pulmonary involvement	8	11	U-MN= 61.5 p=0,008
(Chest CT-scan Total Severity Score)*	(5,25-10)	(9,5-13)	
median (IQ range)			

Discharged home (%)	21 (100)	16§ (64)	nap
ICU admission requiring intubation	0	11	
Death	0	7	

χ^2 = chi square test, U-MN = Mann-Whitney's U Test; °intubated patients were excluded; * CT-scan images at baseline were available for 18 responder and 15 non-responder patients assessed as in references ^{11,12}. §5 patients have been discharged after having treating in ICU. ns=not significant, nap= not applicable

Table 3. Results of logistic regression model incorporating IL-6 at time 24 hours among tested independent variables. Dependent variables: responders vs non responders.

Variables	Regression coefficient B	Standard Error of B	p-value
Age	0.043	0.036	0.234
Sex	-0.061	0.897	0.945
HYQ	0.443	1.671	0.791
LMWH	0.309	0.849	0.716
P/F at baseline	0.036	0.014	0.008
IL-6 at time 24h	-0.002	0.001	0.049

Table 4. Biological characteristics of responder and non-responder patients.

	Responders	Non-Responders	P-value#
IL6° pg/ml at baseline	25	63	U = 88.5
median (IQ range)	(10,775-49,5)	(31,1-93,55)	p=0.020 *
IL6° pg/ml after 24 hours	64	216	U = 79.5
median (IQ range)	(26-196,5)	(159-1012)	p=0.001**
IL6° pg/ml after 72 hours	103	766	U = 40.0
median (IQ range)	(85,5-198,25)	(361-1029)	P<0.001**
vWf°° IU/dl at baseline	257,82	197,48	ns
median (IQ range)	(52,11-622,62)	(107,52-304,45)	
vWf°° IU/dl after 72 hours	153,6	202,97	U = 69.5
median (IQ range)	(107,52-186,51)	(177,18-301,71)	p=0.045 ^
Thrombomodulin°° ng/ml at baseline	7,86	9,48	ns
median (IQ range)	(5,54-9)	(7,44-13,54)	
Thrombomodulin°° ng/ml after 72 hours	6,58	9	ns
median (IQ range)	(4,44-8,46)	(5,76-13,4)	
S-PD°°° ng/ml at baseline	161,97	136,73	ns
median (IQ range)	(116,16-410,32)	(115,8-347,54)	
S-PD°°° ng/ml after 72 hours	319,71	540,15	ns
median (IQ range)	(278,16-501,21)	(364,92-1077,69)	

Mann-Whitney's U Test; °samples for IL-6 at baseline were available in 36 patients, 40 patients at 24h, 35 patients at 72h;°° vWf and Thrombomodulin were tested 30 patients and for vWF in 20 normal controls; °°° S-PD was tested in 20 patients.^ Mann-Whitney's U Test, one-tailed. ns=not significant

Figures

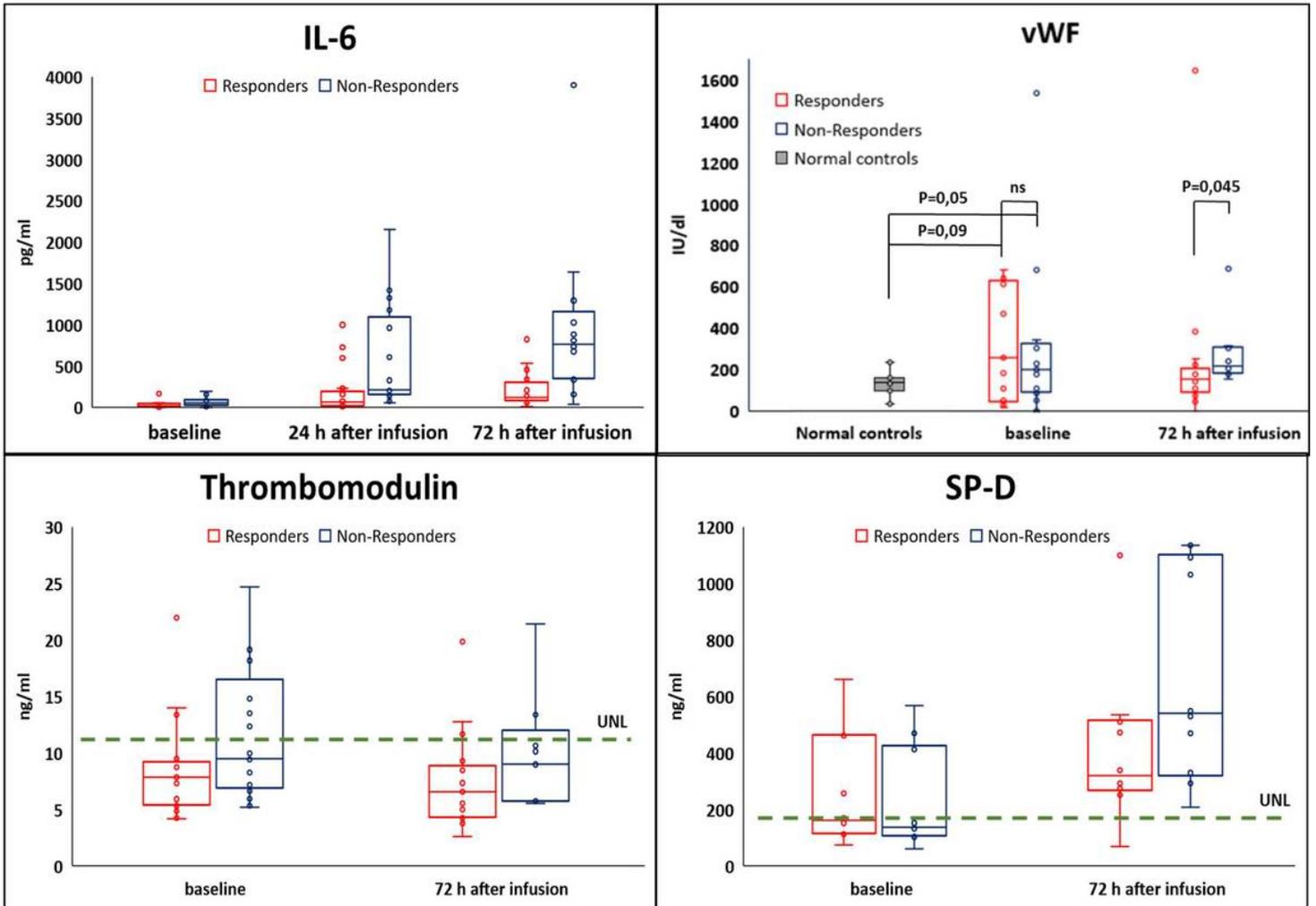


Figure 1

Upper normal limits of reference range at Ospedali Riuniti (Ancona) were IL-6: 5,2 pg/ml, thrombomodulin 11,2 ng/ml and SP-D 190 ng/ml; * and **= p-value reported in Table 4

Supplementary Files

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- [Pomponioetal.tableS1.docx](#)