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Can SSRI/SNRI antidepressants decrease the 'cytokine storm' in the course of COVID-19 pneumonia?

Running title: Interleukin-6 and antidepressants

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ABSTRACT

BACKGROUND Lots of research has been conducted to fight COVID-19 since the outbreak of the pandemic in 2020. The role of 'cytokine storm' in the pathogenesis of COVID-19 pneumonia is well known. Relationship between interleukins and depression is still subject matter of the research, but a correlation between interleukin-6 and depressive disorders is proven by now. The aim of this study is to verify differences among interleukin-6 blood levels of inpatients treated with SSRI and/or SNRI before and during hospitalization and of inpatients not treated with these drugs.

METHODS This is an observational study performed during the first wave of SARS Cov-2 pandemic in Italy for three months. The hospitalized patients of Internal Medicine wards and Infectious and Tropical Diseases ward of Azienda Ospedaliero-Universitaria Careggi of Florence for COVID-19 pneumonia have been divided into two subgroups (treated / not treated with antidepressants). Patients admitted to Intensive Care Unit previously have been excluded. Each patient has been evaluated concerning demographic, clinical and therapeutic features. The first dosage of interleukin-6 detected during hospitalization has been noticed.

RESULTS 8,5% (n=34 patients) of the entire sample (n=402) had been treated with an antidepressant of the two considered categories before admission until discharge from hospital. Significant lower levels of interleukin-6 of recovered patients of the treated subgroup have been highlighted as compared to recovered patients of not-treated subgroup (12,1 vs 25,4 $p<0,001$). These results have been pointed out in spite

of higher mean age and more serious comorbidities of the treated subgroup. Nevertheless the incidence of severe Acute Respiratory Distress Syndrome is significantly lower in the subgroup of patients with antidepressant treatment (20,6% vs 43,2% $p<0,02$) as well as endotracheal intubation employment (0,0% vs 11,7% $p<0,04$). The rate of deceased patients of treated-subgroup is not significant lower than the rate of not-treated subgroup (23,5% vs 26,4% $p=0,13$).

CONCLUSIONS During COVID-19 pneumonia, the production of interleukin-6 seems to be modulated in presence of antidepressant therapy. Further proofs and broader surveys are necessary.

INTRODUCTION

The first wave of SARS Cov-2 pandemic in Italy (2020, from February to June) has been characterized by the rapid COVID-19 spreading and the high death rate [1]. The consequent very serious impact on the Italian National Health Service has to be ascribed to COVID-19 pneumonia with severe acute respiratory distress syndrome (ARDS) and to multi-organ involvement. These diseases are caused in turn by the 'cytokine storm' [2], known also as cytokine release syndrome (CRS), a pathophysiological condition characterized by these features: *elevated circulating cytokine levels, acute systemic inflammatory symptoms, and secondary organ dysfunction beyond that which could be attributed to a normal response to a pathogen, if a pathogen is present* [3] In this condition, inflammatory and immune-pathological mechanisms, mediated by Interferon-γ, interleukin-1, interleukin-6 (IL-6), TNF, and interleukin-18, are involved at the same time, resulting in even systemic acute pro-inflammatory state. Elevated blood levels of these cytokines are detected commonly in the course of CRS [2,4]. IL-6 particularly plays a pathogenic key-role in the course of several internal or autoimmune diseases through CRS mechanism [5]. Therefore IL-6 blocking drugs have been supposed to be effective in the treatment of cykokine storm[6].

Moreover relationships between cytokine system and depression have been found out both in animal models [7-11] and in cross-sectional or metanalytic studies [12-15] in term of elevated blood IL-6 levels in the course of Depressive Disorders.

In details, treatment with selective serotonine reuptake inhibitors (SSRIs) may

decrease IL-6 blood levels and action on the Central and/or Autonomic Nervous System in patients affected by Major Depression Disorder [14]. Mechanisms at the basis of this relationship are still not entirely known [16], but presence of elevated IL-6 levels during chronic stress has been verified comprehensively [5].

Correspondingly, anti-inflammatory effectiveness via cytokine activity modulation added to viral replication inhibition by fluoxetine sometimes [11] has been shown both *in vitro* and in animal models [7-11].

Furthermore an anti-inflammatory action of antidepressants mediated by sigma-1 receptor agonist effect has been highlighted repeatedly [17-20].

A recent randomized, double blind, clinical trial has shown SSRI fluvoxamine induced improvement vs placebo of the respiratory distress in mild COVID-19 patients. This anti-inflammatory effect should be mediated by fluvoxamine agonism on sigma-1 receptor, which modulates the cytokine activity [21]. This result has been confirmed in a recent open-label pragmatic trial recently [22].

Moreover a better prognosis of COVID-19 hospitalized patients if treated by various antidepressants with low affinity for sigma-1 receptor (fluoxetine, paroxetine, escitalopram, venlafaxine and mirtazapine) within 48 h of hospital admission has been showed in a recent observational study [23]. Finally this association between antidepressant therapy and prognosis of COVID-19 has been confirmed in a very recent study [24].

This work presents results of a retrospective observational investigation, approved by

the local Ethics Committee (1704_OSS) of Azienda Ospedaliero-Universitaria Careggi (AOUC) of Florence, regarding inpatients affected by COVID-19 pneumonia during the first wave of the SARS-CoV-2 outbreak in Italy. Those patients were admitted to the Internal Medicine wards and Infectious and Tropical Diseases ward of AOUC from 2020, March, 1st (T0) to 2020, May, 31th (Te). Patients deceased within three months after discharge or during recovery, have been identified. The patients who had been admitted to the Intensive Care Unit (ICU) of AOUC previously, have been excluded from our collection of data. Patients with a COVID-19 infection detected by laboratory methods without radiologic diagnosis of pneumonia by chest radiograph and computed tomography have been excluded too.

The aim of our investigation was to evaluate the possibility that clinical issues and IL-6 blood levels of hospitalized patients with COVID-19 pneumonia might be influenced by antidepressant therapy.

MATHERIALS AND METHODS

Within the sample of COVID-19 patients with pneumonia from T0 to Te, those who had a depressive disorder treated with a selective serotonin reuptake inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressant (AD) at therapeutic dosage before admission to hospital and that had been continuing until the discharge, have been identified (these patients are named '*AD-treated*' in this paper). Diagnosis of these patients were generic ones, such as 'anxious depressive syndrome' or 'depressive syndrome'.

In order to perform an assessment of potential clinical implications of AD therapy both on clinical outcome and on IL-6 activity, the following items which had been routinely collected from all COVID-19 patients upon admission to the hospital, have been examined: age, gender, diagnosis of respiratory failure caused to pneumonia, Horowitz index <200 (sign of ARDS), renal failure that we know as a major comorbidity regarding to prognosis of Covid-19 [21], Charlson Comorbidity Index (CCI), hydroxychloroquine treatment before the admission, the first detected after admission IL-6 blood level performed by IL-6 human instant ELISA kit[1], illness outcome (recovery or death) and the following therapeutic interventions for treatment of COVID-19: corticosteroids, hydroxychloroquine, protease inhibitors, redemsivir, tocilizumab, high flow nasal cannula oxygen (HFNC), non invasive ventilation (NIV), endotracheal intubation, transport of critically ill patients to ICU.

The entire sample has been divided into two subgroups (‘*AD-treated*’ patients and *the* other patients) that have been evaluated according to parameters as above.

Statistical analysis

In order to highlight differences among groups, contingence analysis by Chi-square (χ^2) or Fisher's exact test for categorial variables were carried out. Differences among IL-6 blood levels were evaluated by heteroscedastic Welch's T analysis (two tails). Differences between both CCI scores and ages of each subgroups were evaluated by Mann-Whitney U test for non-parametric data. The level of statistical was set at

[1] IL-6 performed by a different method (patients: n=5) have not been evaluated in this study.

P<0,05.

RESULTS

The total sample is composed by 402 inpatients aged between 21 and 100 (mean age=70,0), 162 (40,3%) of which are female (mean age=73,2) and 240 (59,7%) are male (mean age=67,9). 34 of those ones (8,5% of the total sample) have been identified as treated with an antidepressant drug (SSRI: sertraline: n=9; escitalopram: n=8, citalopram: n=5, paroxetine: n=5; SNRI: venlafaxine: n=3, duloxetine: n=3; SSRI+SNRI: escitalopram+venlafaxine: n=1) according to the above-mentioned criteria. Antidepressants' dosages were lower than respective fluoxetine-equivalent ones.

Demographic features and outcomes of AD-treated subgroup (n=34) compared with the other patients (n=368) are summarized in Table 1. A not significant majority of female and a significant higher mean age (=80,1) emerge clearly, especially if patients that are 75 or older are taking into account in each subgroup (61,8% vs 28,8% p<0,001). Regarding illness outcome, the two subgroups do not differ significantly (p=0,13) even if slightly majority of recovered patients (76,5% vs 73,6%) and slightly minority of deceased patients (26,5% vs 23,4%) within AD-treated subgroup have been highlighted. Clinical conditions and therapeutic procedures are summarized in Table 2. Respiratory failure related to pneumonia does not differ between the two subgroups although the rate of ARDS is significantly lower for the AD-treated subgroup (20,6% vs. 43,2% p<0,02). Regarding

comorbidities, *AD-treated* subgroup is characterized by very significantly higher CCI scores (6,7±2,5 vs. 3,9±2,8 p<0,005). Renal failure as a comorbidity does not differ from the other patients. Therapeutic procedures do not seem distinguish particularly except for a mild significant lower employment both of protease inhibitors (64,7% vs 80,2% p<0,04). and endotracheal intubation (0,0% vs 11,7% p<0,04) in AD-treated patients. In this subgroup a mild significant higher use of hydroxychloroquine before admission emerges to be carried out (11,8% vs 3,3% p<0,04).

371 patients (92,3% of the entire sample: 32 AD-treated and 339 others, 94,1% and 92,1% respectively, not significant difference according to Fisher's Exact test) have been evaluated with regard to IL-6 levels as considered in this study (see above). IL-6 values of 26 patients were not detected during hospitalization and IL-6 values of 5 patients were detected by different laboratory method.

Within our sample, IL-6 blood levels (Table 3) are able to discriminate recovered patients from died of the total sample, its values turning out to be higher significantly in the latter ones. Similar significant relationships are pointed out taking into consideration recovered patients of the two subgroups, but not considering deceased patients. If IL-6 blood levels of pneumonia without or with respiratory failure are taken into consideration as a whole respectively, significantly higher values are pointed out in patients with respiratory failure. Furthermore, slightly significant (p<0,04) lower values are pointed out in recovered patients without respiratory failure of the AD subgroup. Moreover, if we compare IL-6 values of the patients without or with respiratory failure distinguishing AD-treated patients from other ones, slightly

significant lower values ($p<0,04$) and significant ones ($p<0,002$) respectively for recovered patients of the former subgroup are highlighted. Finally (Table 3), an almost significant reduction in IL-6 blood levels (7,9±7,5 vs 33,4±61,1 $p=0,056$) has been observed in patients treated by antidepressant with moderate affinity for sigma-1 receptor (sertraline in our sample) as compared to patients treated by antidepressants with low affinity (all the other ones) [26].

DISCUSSION

Two issues arise clearly from results of our study: the former is the strict relationship between IL-6 blood levels and illness outcome as expected (see Introduction), in term of almost steady lower levels in recovered patients.

The latter is a trend to lower IL-6 values in the AD-treated subgroup as compared to those of the other patients. This tendency is confirmed also examining the two subgroups in relation to the risk of respiratory failure due to pneumonia. Despite these data, mortality rate within the AD-treated subgroup is not lower than in the other patients of the sample. Explaining this issue is not simple. First of all the numerousness of the AD-treated subgroup is small (8,5% of the total sample). This percentage is very similar to the rate of employment of antidepressants (8,22%) within the general population of Tuscany in 2019 [27], but comparison appears difficult: AD-treated patients subgroup show high mean age and high size of medical comorbidities. These features make a subject more likely to develop depression and to be treated by an antidepressant [28]. So our AD-treated subgroup cannot be

considered representative of general population of Tuscany. Secondly health conditions of our patients with antidepressant therapy appear to be worse than those of the other patients: the rate of comorbidities is significantly higher and the role of comorbidity in the course of COVID-19 and its impact on prognosis are well-known [25]. AD-treated patients received the same therapy of the other patients during hospitalisation and this fact may increase the risk of death in presence of more numerous comorbidities; the only exception has been the significant higher use of hydroxychloroquine before admission, but this may be related to assiduous care within the scope of medical domestic activity. Moreover AD-treated patients of our sample are significantly older on average than the other patients, especially if the age of 75 or over is taken into account. This issue may have had an impact on mortality of this subgroup. Finally IL-6 levels point out a noteworthy amount of variability with consequent very high standard deviation especially in deceased patients (due to 'cytokine storm'?). So statistical analysis may get effortless in case of small numerousness as in AD-treated patients.

Anyway IL-6 values of recovered AD-treated patients have been lower within each comparison of our sample. This fact might be reason for significant lower risk of ARDS, significant lower employment of endotracheal intubation and significant lower choice of transport to ICU for AD-treated subgroup as compared with the other patients.

The significant decrease of IL-6 values in AD-treated subgroup may be explained by the Functional Inhibition of AcidSphyngomielinase induced by antidepressants [29-

31]. This inhibition reduces intra-cellular ceramides which in turn can boost viral way in the host's cell. So this mechanism mediated by antidepressant drugs may result in reduction of inflammation due to SARS-Cov-2 (including cytokines concentration).

Finally our results do not allow to confirm or not the role of fluvoxamine in improving COVID-19 outcome as pointed out by other studies [11,17,20-23], because of lack of fluvoxamine-treated patients in our sample.

All the results of our study have to be taken into consideration with extreme caution because of limitations of our study: little number and precarious health conditions of AD-treated patients as well as their advanced age. All these issues might make them not comparable easily to other patients of our sample. Moreover data for this investigation were detected immediately after the SARS-CoV-2 outbreak in Italy, and this, inevitably, may entail some criticality, for example not to have evaluated the levels of other cytokines routinely.

Finally use of antidepressants during COVID-19 is a relevant matter given the fact that the impact on mental health is and will be an hard problem for involved communities. [32]

CONCLUSIONS

The data that were gathered for this study seem to confirm the role of certain antidepressants' categories in modulating the IL-6 production.

Randomized double-blind and broad observational survey are necessary in order to evaluate the impact of antidepressant therapy on prognosis of SARS-Cov2 illness.

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TABLE 1: Demographic and outcome features

Total sample: n= 402

Female= 162 (40,3%) **Male 240= (59,7%)**

Mean age= 70,0 (female=73,2; male=67,9)

***AD-treated* patients**		***The* other patients**		**P**
n: 34 (8,4%)		**n: 368 (91,6%)**		
female	**male**	**female**	**male**	
19 (55,9%)	15 (44,1%)	143 (38,9%)	225 (61,1%)	χ^2=3,75 p=0,053 NS
age		**age**		
mean=80,1		**mean =69,1**		**U=3664,5; z score= -3,99707 p<0,001**
female	**male**	**female**	**male**	
79,9	81,1	72,4	67,0	
Age≥75				
21 (61,8%)		106 (28,8%)		**χ^2=15,65 p<0,001**

Illness outcome

Recovery: 297 (73,9%) vs. Mortality: 105 (26,1%)

***AD-treated* patients**	***The* other patients**	
Recovered: 26 (76,5%)	**Recovered: 271 (73,6%)**	
		χ^2: 0,13 NS
Deceased: 8 (23,5%)	**Deceased: 97 (26,4%)**	

TABLE 2: Clinical and therapeutics features

AD-treated patients	*The* other patients	
Respiratory function		
normal: 108 (26,9%) vs. failure: 294 (73,1%)		
AD-treated: 7 (20,6%) others: 101 (27,4%)	**AD-treated: 27 (79,4%) others: 267 (72,5%)**	χ^2: 0,74 NS
recov. 7 dec. 0 recov. 89 dec. 7		Fisher: 0,6 NS
	recov. 19 dec. 8 recov. 182 dec. 19	χ^2: 0,05 NS
Comorbidities		
Charlson Comorbidity Index (CCI)	**6,7±2,5**	**3,9±2,8**	**U=4271,5; z score= -3,06067 p<0,005**
Renal failure	n: 5 (14,7%)	n: 48 (13,0%)	Fisher 0,79 NS
Clinical conditions			
ARDS Horowitz <200	n: 7 (20,6%)	n: 159 (43,2%)	**χ^2: 6,57 p<0,02**
Therapeutic actions			
Hydroxychloroquine before admission	n: 4 (11,8%)	n: 12 (3,3%)	**Fisher: <0,04**
Hydroxychloroquine	n: 27 (79,4%)	n: 324 (88,0%)	Fisher 0,17 NS
Protease inhibitors	n: 22 (64,7%)	n: 295 (80,2%)	**Chi: 4,46 p<0,04**
Steroids	n: 10 (29,4%)	n: 118 (32,1%)	χ^2: 0,10 NS
Redemsivir	n: 0 (0%)	n: 14 (3,8%)	Fisher 0,39 NS
Ruxolinib	n: 5 (14,7%)	n: 26 (7,1%)	Fisher 0,17 NS
Tocilizumab	n: 2 (5,9%)	n: 64 (17,4%)	Fisher 0,09 NS
high flow nasal cannula oxygen (HFNC)	n: 2 (5,9%)	n: 58 (15,8%)	Fisher 0,14 NS
non invasive ventilation (NIV)	n: 4 (11,8%)	n: 72 (19,6) %	Fisher 0,36 NS
endotracheal intubation	n: 0 (0%)	n: 43 (11,7%)	**Fisher<0,04**
transport to ICU	n: 2 (5,9%)	n: 57 (15,5%)	Fisher 0,20 NS

TABLE 3: Interleukin-6

IL-6 values (pg/ml): mean±standard deviation

IL-6 vs illness outcome		P
Recovered patients	**Deceased patients**	t= 3,462
24,2±37,5	**54,9±81,4**	**p<0,001**
***AD-treated* patients vs *The* other patients**		
Total: 27,0±54,0	Total: 32,1±53,3	t= 0,502 NS
Recovered: 12,1±12,7	Recovered: 25,4±39,0	t= 3,811 **p<0,001**
Deceased: 91,4±105,4	Deceased: 52,3±79,6	t= 0,020 NS

IL-6 vs respiratory function				P	
Normal		**Failure**			
total		**total**		t= 4,094	
17,3±30,6		36,9±58,6		**p<0,001**	
AD-treated	**others**	***AD-treated***	**others**	t=2,269	t=0,024
7,2±7,7	16,8±31,2	32,5±60,0	32,2±53,3	**p<0,04**	NS
***AD-treated* recovered**	**others recovered**	***AD-treated* recovered**	**others recovered**	t= 2,251	t= 4,25
7,2±7,7	17,7±33,2	13,9±13,9	29,1±41,1	**p<0,04**	**p<0,002**

Antidepressant with moderate vs weak affinity for sigma-1 receptor				P	
IL-6 values		**deceased AD-treated (%)**			
sertraline	**other ADs**	**sertraline**	**other ADs**	t=2,0	Fisher:
7,9,±7,5	33,4±61,1	n=6 (33,3)	n=5 (20,0)	p=0,056 NS	0,65 NS

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