Dual-Histamine Blockade with Cetirizine - Famotidine Reduces Pulmonary Symptoms in COVID-19 Patients

Running Title: Treatment of COVID-19 with Cetirizine - Famotidine

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Conflicts of Interest: Dr. Hogan II discloses a US patent application on dual-histamine blockade in the treatment of COVID-19 and issued patents on the treatment of diarrhea, plus ownership in a biomedical business related to the latter; Dr. Cannon has nothing to disclose; Dr. Rappai

has nothing to disclose; Dr. Studdard reports personal fees from American College of Chest Physicians, unrelated to the submitted work; Dr. Hogan III has nothing to disclose; Dr. Paul discloses ownership in unrelated biomedical-related businesses and consulting with numerous pharmaceutical companies; and Dr. Dooley discloses ownership in unrelated biomedical-related businesses.

Abstract

Background: The COVID-19 pandemic due to SARS-CoV-2 infection can produce Acute Respiratory Distress Syndrome as a result of a pulmonary cytokine storm. Antihistamines are safe and effective treatments for reducing inflammation and cytokine release. Combinations of Histamine-1 and Histamine-2 receptor antagonists have been effective in urticaria, and might reduce the histamine-mediated pulmonary cytokine storm in COVID-19. Can a combination of Histamine-1 and Histamine-2 blockers improve COVID-19 inpatient outcomes?

Methods: A physician-sponsored cohort study of cetirizine and famotidine was performed in hospitalized patients with severe to critical pulmonary symptoms. Pulmonologists led the inpatient care in a single medical center of 110 high-acuity patients that were treated with cetirizine 10 mg and famotidine 20 mg *b.i.d.* plus standard-of-care.

Results: Of all patients, including those with Do Not Resuscitate directives, receiving the dual-histamine blockade for at least 48 hours, the combination drug treatment resulted in a 16.4% rate of intubation, a 7.3% rate of intubation after a minimum of 48 hours of treatment, a 15.5% rate of inpatient mortality, and 11.0 days duration of hospitalization. The drug combination exhibited reductions in symptom progression when compared to published reports of COVID-19 patients. Concomitant medications were assessed and hydroxychloroquine was correlated with worse outcomes.

Conclusions: This physician-sponsored cohort study of cetirizine and famotidine provides proof-of-concept of a new safe and effective method to reduce the progression in symptom severity, presumably by minimizing the histamine-mediated cytokine storm. Further clinical

studies in COVID-19 are warranted of the repurposed off-label combination of two historically-safe histamine blockers.

Key words: COVID, ARDS, histamine, antihistamine, lung, cytokine storm, treatment

Introduction

Histamine and mast cells play a fundamental role in modulating inflammation through increased capillary blood flow and vascular permeability, as well as cytokine release. Histamine-1 (H1) receptor antagonists (e.g., cetirizine) are administered for allergies. Histamine-2 (H2) receptor antagonists (e.g., famotidine) are used to control heart burn. Prescription branded, generic, and over-the-counter (OTC) drugs of both classes are safe and commercially available worldwide.

Humans have been treated using dual-histamine blockade. Urticaria (hives) has been successfully treated with dual-histamine blockade since the 1970's [1-3]. And, a few reports have begun to demonstrate that diarrhea can be treated similarly [4,5]. At present no H1-H2 combination drug has been US FDA-approved.

COVID-19 (SARS-CoV-2) emerged in late 2019 in China, and nucleic acid sequence results indicate that it was very likely from a bat vector. The disease can manifest as a hyper-immune response with pulmonary cytokine release resembling that of other respiratory infections, such as Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and influenza. Studies from China have defined the COVID-19 cytokine profile [6] and identified risk factors that increase mortality [7]. These retrospective studies suggest mortality may be linked to inflammatory processes caused by a "cytokine storm", which was very common in patients with severe to critical symptoms [8]. Pulmonary pathology in early-phase COVID-19 pneumonia has

shown acute lung injury [9]. In the later stage of disease, patients can develop Acute Respiratory Distress Syndrome (ARDS) or ARDS-like conditions and multi-organ failure [10].

According to the Centers for Disease Control (CDC), the disease severity from China is 14% severe and 5% critical, and the critical patients displayed a fatality rate of 49%. (www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html). Furthermore the CDC reports, "*Among U.S. COVID-19 cases with known disposition, the proportion of persons who were hospitalized was 19%. Among all hospitalized patients, a range of 26% to 32% of patients were admitted to the ICU. Among all patients, a range of 3% to 17% developed ARDS compared to a range of 20% to 42% for hospitalized patients and 67% to 85% for patients admitted to the ICU. Mortality among patients admitted to the ICU ranges from 39% to 72% depending on the study. The median length of hospitalization among survivors was 10 to 13 days.*"

Because of the sudden emergence of COVID-19, rapid research efforts are being conducted to repurpose existing drugs or biologic immunotherapies, as these are more likely to have near-term benefit during the pandemic. A major goal of many of these initiatives is to prevent or reduce the cytokine storm in pulmonary tissue [11-13].

Animal model studies are informative at this juncture. Sars-CoV-infected mice have shown that T-cell responses are required for protection from disease and for virus clearance [14]. The immunomodulation by histamine depends mostly on its influence of T-cells [15]. Histamine

stimulates inflammation, cytokine release, and can lead to tissue damage, including lung [16]. A porcine study evaluating H1N1 influenza demonstrated the accumulation of histamine in severe pneumonia [17]. Furthermore, the histamine H1 receptor antagonist, ketotifen, decreased inflammatory cytokines and severe pneumonia [17].

Dual-histamine blockade has been effective in animal models of bacterial ARDS and allergy. A porcine animal model study has shown successful treatment of Pseudomonas-induced ARDS with diphenhydramine and cimetidine [18]. In this model for the treatment of hypoxemia, pulmonary hypertension, and pulmonary microvascular injury, the combination of diphenhydramine and cimetidine was essential, and was augmented somewhat by ibuprofen. In a guinea pig model, treatment with clemastine and cimetidine protected against allergen-induced bronchial obstruction [19].

Therefore, we believe it is reasonable to bridge into humans infected by COVID-19 using dual-histamine blockade, in order to prevent or diminish the cytokine storm. Furthermore, the safety and efficacy of dual-histamine blockade previously evidenced in human urticaria (and diarrhea) makes this an appealing approach. Therefore, the major goals of the present proof-of-principle study include to decrease the progression of severe and critical (high-acuity) hospitalized patients to ventilation dependence and/or death.

Methods

This physician-sponsored cohort study was led by a team of board certified pulmonologists from a single practice group in Jackson, MS. All patients were treated in a single hospital operated by Baptist Health Systems, with IRB approval (IRB # 20-49 exemption) for retrospective access to patient data. The first dual drug-treated patient date was 3 April 2020 and the study period for this cohort concluded on 13 June 2020. The study was motivated by the principle of compassionate care use of repurposed medications (in view of the rationale, above) by the attending pulmonologists during the COVID-19 pandemic. Conditions included open-label drug use, without a placebo control or randomization. In lieu of a placebo control group, for comparison the control(s) consisted of published SOC patient results that were not administered the dual-histamine blockade from the USA and China.

Inclusion and Exclusion Criteria: The inclusion criteria were: (a) Males or females of minimum age of 17; (b) Admission to the hospital with suspected or confirmed pulmonary symptoms of COVID-19. All patients were confirmed COVID-19 positive by RT-PCR within several days of admission. The exclusion criteria were: (a) The patient is negative for COVID-19 by RT-PCR diagnostic test; (b) Sensitivity or allergy to cetirizine or famotidine, if known; (c) Duration of stay of less than 48 hours; and (d) Treatment with the drug combination for less than 48 hours. The investigators anticipated that any patient who was subject to a Do Not Resuscitate (DNR) directive may be a confounding factor (e.g., with regard to old age or the extent of aggressive life-sustaining care provided). Therefore, the DNR patients' results were parsed in the analyses for comparison to all patients.

Standard-of-Care Procedures & Medications: On admission to hospital, the patient was diagnosed for suspected COVID-19 based primarily upon pulmonary symptoms, and located within a COVID-19 ward. Treatment was initiated in ER with SOC per admitting provider. The patient was confirmed positive for COVID-19 by RT-PCR diagnostic test. SOC included radiologic assessments, supplemental oxygen when necessary, and intravenous (IV) hydration when necessary. SOC concomitant treatments included the antimalarial drug hydroxychloroquine (84.5%), the anti-IL6 biologic tocilizumab (50.9%), the glucocorticoid drug methylprednisolone (30.9%), and convalescence plasma (30.0%). The cumulative rate of intubation in this cohort was 16.4%.

Cetirizine - Famotidine Treatment: The H1 receptor antagonist was cetirizine. The H2 receptor antagonist was famotidine. Given the current challenge of market availability of oral H2 antagonists, whenever the oral dosage form was not available or appropriate the clinicians used famotidine IV. Cetirizine and famotidine administration was preferably (a) oral, when feasible; then (b) gastric via nasogastric tube; then (c) by IV injection, based upon clinical assessments. The first dose of the therapy was administered in the ER, or upon arrival to the COVID ward, or when our trial started. Famotidine 20 mg IV and cetirizine 10 mg IV (or alternatively PO) was administered. Subsequent doses consisted of famotidine 20 mg q 12 hrs and cetirizine 10 mg q 12 hrs PO.

Study Endpoints: The major endpoints were: (a) Increased rate of discharge; (b) Reduced ventilation requirements (i.e., reduced number of intubations overall and after receiving a

minimum of 48 hours of dual drug treatment); (c) Reduced inpatient mortality rate; and (d) Reduced duration of hospitalization.

The study endpoints were compared to SOC patient outcomes from Atlanta, GA [20], Louisiana [21], New York City, NY [22], and Wuhan, China [23,24]. This comparison to external sources is informative, as the number of available SOC-only patients was limited in this medical center during the rapidly-evolving SOC in the COVID-19 pandemic. This new dual drug treatment paradigm was rapidly adopted as SOC in this hospital.

Results

The patient demographics for the cetirizine - famotidine treatment group consisted of 110 patients age 17 to 97; mean age of 63.7 (SD 18.1); Female 59% and male 41%; and racial composition of 36.4% White, 59.1% African American or Black, 4.5% other. According to the US Census Bureau the racial demographics for the state of Mississippi are 59.1% White, 37.8% African American or Black, 3.1% other, and the median age is 36.7 years. Thus, our treated patients in this medical center represented an inversion in racial demographics with regard to the state's statistics vis-à-vis African-American or Black versus White.

The 110 COVID-19-positive patients with severe and critical pulmonary symptoms were treated in an inpatient setting with cetirizine and famotidine for a minimum of 48 hours, in addition to SOC. This group of patients manifested an average of 2.7 comorbidities (**Table I**). The most

common comorbidities were hypertension (78.2%), obesity plus morbid obesity (58.2%), diabetes (42.7%), and cardiac disease (26.4%).

The results of dual drug treatment are summarized with regard to all patients including DNR and the subset excluding DNR (**Table II**). The investigators anticipated DNR patients would be a confounding factor, and there were 13 DNR patients. The endpoints were: (a) discharge rate; (b) intubation rate; (c) intubation rate after a minimum of 48 hours of dual drug treatment; (d) inpatient mortality rate; and (e) average number of days to discharge. The rate of discharge during the study period (10 weeks plus 1 day) was 84.5% (and 91.8% excluding DNR). The intubation rate was 16.4% (and 16.5% excluding DNR). The intubation rate after a minimum of 48 hours of drug treatment was 7.3% (and 6.2% excluding DNR). The inpatient mortality rate was 15.5% (and 8.2% excluding DNR). The average number of days to discharge was 11.0 (and 10.9 days excluding DNR).

Concomitant administration of other drugs, biologics, or treatments in the SOC of the severe to critical patients are potential confounding factors (**Table III**). For instance, 84.5% of the patients were administered hydroxychloroquine (HCQ). Based upon recent publications [25-27], one may assert that HCQ likely provided no therapeutic benefit, and might have had an adverse effect on the outcomes in this cohort of 110 patients, as it correlated with worse outcomes (i.e., higher rates of intubation and death).

In some of the patients, and especially those who progressed to ventilation dependence, a biologic (tocilizumab in 50.9% of patients), a glucocorticoid (methylprednisolone in 30.9% of patients), or convalescent plasma (in 30.0% of patients) were used at the discretion of the

pulmonologist-led critical care team as concomitant treatments (**Table III**). At those junctures in patient management, the concomitant treatments were anticipated to possibly provide some benefit to the patients. However, the high degree of correlation of use of methylprednisolone, tocilizumab, and/or convalescent plasma with intubation per se hampered measurement.

It is interesting to note the clinical nature of the intubated patients and deaths associated with intubation. Of the 18 intubated patients, 9 died (50.0%). Of the group of 10 patients intubated prior to completing 48 hours of combination drug therapy, 9 were subsequently successfully extubated, 5 of whom were extubated within 2 to 4 days. Of the 8 patients intubated after completing a minimum of 48 hours of cetirizine and famotidine use, all 8 patients died and all received tocilizumab and convalescence plasma, whereas only 2 of the 8 patients received methylprednisolone. This particular patient subpopulation (n = 8) was critically ill and included 2 leukemia patients, a cirrhotic patient, a 91 year old with chronic kidney disease, a 79 year old former smoker with chronic kidney disease stage 3, an end stage renal disease patient, and a multiple sclerosis patient with chronic kidney disease in cardiogenic shock.

Limitations

There are multiple limitations to any physician-sponsored cohort (or case series) study. Within this initial study the limitations were most notably: (a) This proof-of-principle study was not a prospective, placebo-controlled, randomized, and blinded study that is customary for a regulatory registration trial; and (b) The study lacked a sufficiently high number of untreated

SOC patients for use as a retrospective control cohort. However, the investigators have provided comparisons to the published SOC cohorts from other regions in the USA and China.

However, offsetting these limitations it should be noted that this work was performed in April through June 2020 during an intense season within the COVID-19 pandemic crisis, at a time-is-of-the-essence season when pulmonologists, emergency room physicians, critical care specialists, and hospitalists were eager to attempt rational repurposing of previously FDA-approved medications. Thus, the physicians desired near-term improved outcomes, compassionate care, and to identify new proof-of-concept off-label therapies for COVID-19 ARDS patients. This resulted in the vast majority of all COVID-19 positive patients in this medical center being treated with cetirizine plus famotidine as the “new” SOC.

Discussion and Conclusions

Here we describe an initial study of dual-histamine blockade to retard the histamine-cytokine network and with the intention of blunting the cytokine storm. The safety profile of dual-histamine blockade makes this an appealing consideration for COVID-19-positive patients. If dual-histamine blockade is able to blunt the cytokine system, the risk of progressing to severe and/or critical disease should lessen.

The results of this initial physician-sponsored study provide a proof-of-principle that it can reduce disease severity and the need for ventilators, and save lives. The results of patients who received at least 48 hours of the combination drug treatment demonstrated reduced rates of intubation (16.4%), of intubation after 48 hours of dual drug treatment (7.3%), of inpatient mortality (15.5%), and of duration of hospitalization (11.0 days). If DNR patients were excluded, then the inpatient mortality rate was only 8.2%. These clinical outcomes represent reductions in the anticipated symptom severity expressed as ventilator dependence and lethality relative to SOC reported in Atlanta, Georgia [20], Louisiana [21], New York City, New York [22], and Wuhan, China [23,24] (see below).

Outside of the dual-histamine blockade cohort group, preliminary results were noted by the same group of pulmonologists in the same medical center with an independent group of 12 SOC-only COVID-19 patients. The SOC-only patients (lacking cetirizine and famotidine) resulted in 5 intubations (41.7%), 5 deaths (41.7%), and 18.0 average days to discharge (data not shown). These SOC-only preliminary results are consistent with high symptom severity and

high rate of inpatient fatality in the overall admitted patient population. Furthermore, a small group of 7 famotidine-only patients resulted in 3 intubations (42.9%), 1 death (14.3%), and 16.2 average days to discharge (data not shown). Due to the limited number of patients in each of these two groups, they were not deemed sufficient for comparative analysis, relative to 110 cohort patients receiving cetirizine and famotidine for a minimum of 48 hours.

The 15.5% inpatient fatality rate or 8.2% excluding DNR patients compares favorably to a published inpatient fatality rates from other regions -- 25.8% in Atlanta, GA [20], 23.6% in Louisiana [21], 21% in New York City, NY [22], and 21.9 and 28.3% in Whuan, China [23,24]. In other words, we experienced a reduction in inpatient fatalities of approximately one fourth to one third relative to these reference locations.

The reports of inpatient mortality rate can be dependent on multiple variables, such as inclusion/exclusion criteria (e.g., regarding DNR patients), diagnosis (e.g., presumptive COVID-19 vs. PCR-confirmed for viral RNA), demographics of patients in the study, the duration of the study period, symptom severity and comorbidities at the time of admission, as well as rapidly evolving SOC treatments influenced by media, governmental agencies, and clinical reports. During this crisis it should be noted that many of the "publications" on COVID-19 were available only in preprint form, in view of time-is-of-the-essence. And, in some instances the information was only presented as an assertion in the media, without any supporting scientific information.

That being said, in our cohort 17 fatalities had an average age of 70.6 and our 9 DNR deaths had an average of 75.8 years. *[Note that one DNR death was due to a cirrhotic patient aged 38; if this individual had been excluded the DNR deaths would have averaged 80.5 years.]* Our overall and DNR deaths were predominantly among the elderly. Furthermore, the small group of 12 SOC-only patients treated by our pulmonologists exhibited a high case fatality rate of 41.7% in the same medical center (data not shown). These two findings (i.e., elderly patient deaths and a small SOC-only group with a high rate of inpatient fatality), suggest that our inpatient fatality rate of 15.5% with DNR was adversely impacted by patient age and multiple comorbidities (average of 2.7) in Central Mississippi. In other words, our dual-histamine blockade treatment effects were favorable even in an unfavorable context.

With regard to ventilator dependence, the observed intubation rate of 16.4% overall in the cohort of 110 patients (including DNR directives) in Jackson, Mississippi and especially only 7.3% intubation rate after a minimum of 48 hours of treatment with cetirizine plus famotidine compares favorably to 26.3% in Louisiana [21], 12.2% in New York City [22], and 33.3% in Wuhan, China [23].

How does this H1-H2 drug combination treatment compare with other recent therapeutic developments in COVID-19? There are three noteworthy examples that have received attention at this juncture in the scientific literature and media, namely hydroxychloroquine, remdesivir, and famotidine.

First, hydroxychloroquine (HCQ) rapidly received general acceptance as a SOC medication for COVID-19 patients. The risk-benefit reward analysis of HCQ rapidly evolved to a highly unfavorable impression, based upon controlled clinical trials. The efficacy of HCQ in COVID-19 is now seriously doubted, and at least one cardio-toxic side effect has been noted [25]. This study consisted of 75 patients per arm, comparing SOC vs SOC + HCQ. The authors concluded that HCQ was not beneficial and resulted in more adverse events. Hydroxychloroquine was also ineffective in inpatients who required oxygen; 84 patients were treated with HCQ within 48 hours of admission vs 97 patients receiving SOC without HCQ [27]. There were no benefits to HCQ when assessing: (a) survival without transfer to ICU; (b) survival at 21 days; (c) survival without ARDS at 21 days; and (d) percentage of patients requiring oxygen at 21 days. Furthermore, 10% of the HCQ-treated patients manifested ECG anomalies requiring discontinuation of HCQ treatment. A randomized trial of hydroxychloroquine in COVID-19 patients attempted to detect a prophylactic benefit, and it was unsuccessful [26]. In aggregate these studies confirm that HCQ was not effective in preventing or treating disease progression in COVID-19 patients. The US FDA rescinded the Emergency Use Authorization (EUA) for this drug. Therefore, it should be noted that HCQ was administered to most of the patients in our study, and it is reasonable to speculate that it impaired patients in our cohort, in view of the correlation with worse outcomes.

Second, remdesivir was developed prior to the COVID-19 pandemic as a retroviral replication inhibitor. A well-designed placebo-controlled trial suggested a reduction in the time to clinical

improvement [28]. However, the study was not sufficiently powered statistically [29]. Thus, there was no improvement with regard to patient deaths or viral load. This trial did not provide convincing evidence of a substantial therapeutic benefit of remdesivir. Regardless, the US FDA granted EUA for this prescription medication, which is expected to be expensive in the USA.

And third, famotidine has been evaluated in a large retrospective association study of COVID-19 patients in New York City [30]. A total of 84 hospitalized patients out of 1,620 total received famotidine within 24 hours of hospitalization. The doses ranged from 10-40 mg. Famotidine use was associated with a reduced risk of death or intubation, whereas by comparison proton pump inhibitors (that reduce gastric acid independent of a histamine mechanism) were not associated with reduced risk of death or intubation. This suggests a possible histamine-mediated effect in the COVID-19 patients. The authors also noted no benefit of HCQ. In addition very high doses of famotidine have been proposed elsewhere for COVID-19 outpatients [31]. A case series of only 10 outpatients administered high dose famotidine (most of them received 80 mg t.i.d. = 240 mg daily) perhaps suggested the possibility of a benefit [31]. For comparison our inpatient study of 110 patients used only 20 mg b.i.d. (40 mg daily) of famotidine, within the FDA-approved OTC dosage levels. The cetirizine amount (10 mg b.i.d.) is double the daily FDA-approved dosage as an OTC medication.

Given (a) the recent emergence of COVID-19, (b) the rapid need for safe and effective treatments deployable immediately, and (c) the rapid evolution in the SOC treatments, recent

innovations might not permit sufficient time for the statistically robust clinical trials that are customary for an FDA regulatory approval process. In this time-is-of-the-essence pandemic context, the results of this dual-histamine blockade treatment compares favorably to current SOC patients.

Although this study provides initial evidence in support of a safe and effective treatment, many questions remain to be addressed. Randomized prospective trials are warranted with inpatients and outpatients. We have planned a randomized placebo-controlled outpatient trial to begin to address this question in PCR-confirmed asymptomatic or mild-to-moderate severity patients. Furthermore, is the beneficial effect dependent on this particular combination of active pharmaceutical ingredients? And, would some patients benefit (more) from alternative doses or dosage schedules? It would also be highly beneficial to exclude HCQ as a confounding factor in prospective trials, as it might have been a handicap to our cohort

The present clinical investigation provides a new method of treatment for this unmet medical need. If the results reported here are replicated in other trials, the medications can provide safe and effective means to rapidly affect patient outcomes worldwide, which are anticipated to save lives. The favorable circumstances of having commercially-available branded, generic, and OTC drugs of both H1 and H2 receptor types provides another distinct advantage relative to other experimental drug and biologic research programs in COVID-19, some of which may take numerous years to develop and commercialize. This new approach could be rapidly deployed worldwide and should be affordable, even for under-served populations, not just for the economically advantaged.

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Table I: Comorbidities in 110 hospitalized COVID-19 patients treated with famotidine and cetirizine for a minimum of 48 hours

Comorbidities:	%
Diabetes	42.7%
Hypertension	78.2%
COPD	13.6%
Cardiac Disease	26.4%
Arrythmia	16.4%
Asthma	10.9%
Smoker	20.0%
Obesity (excluding Morbid Obesity)	41.8%
Morbid Obesity	16.4%
Total Comorbidities Per Patient	Mean = 2.7

Table II: Clinical outcomes in 110 hospitalized COVID-19 patients treated with famotidine and cetirizine for a minimum of 48 hours

Key Metric:	Including DNR	Excluding DNR
Total Patients Admitted	110	97
Total Patients Discharged	93	89
Discharge Rate	**84.5%**	**91.8%**
Total Patients Intubated	18	16
Intubation Rate	**16.4%**	**16.5%**
Total Patients Intubated After a Minimum of 48 hrs of Treatment	8	6
Intubation Rate After a Minimum of 48 hrs of Treatment	**7.3%**	**6.2%**
Total Deaths	17	8
Death Rate %	**15.5%**	**8.2%**
Average Days to Discharge	**11.0**	**10.9**

Table III: Clinical outcomes in 110 famotidine and cetirizine-treated COVID-19 patients and concomitant treatments

Concomitant Treatments	Total #	% of Total	Intubated %	Death %
Hydroxychloroquine - YES	93	84.5%	18.3%	17.2%
Hydroxychloroquine - NO	17	15.5%	5.9%	5.9%
Methylprednisolone - YES	34	30.9%	29.4%	14.7%
Methylprednisolone - NO	76	69.1%	10.5%	15.8%
Tocilizumab - YES	56	50.9%	30.4%	21.4%
Tocilizumab - NO	54	49.1%	1.9%	9.3%
Convalescent Plasma - YES	33	30.0%	30.3%	33.3%
Convalescent Plasma - NO	77	70.0%	10.4%	7.8%