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Case Report

Positive Impact of the antimicrobial drug on Survival and Recuperation Times in Patients with COVID-19.

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Abstract

Few papers that describe the diagnostic performance of serological tests for Campylobacter spp. were found in our search of the literature. Just 13 papers were chosen for examination out of the 133 that were found using manual searches and databases. These papers primarily describe the outcomes of serological tests using complement fixation, immunochromatography, and enzyme immunoassay to detect Campylobacter spp. Most regions of the world are seeing an increase in campylobacter infections. The list of nationally notifiable diseases was expanded to include campylobacteriosis in 2015 [24]. However, due to the lack of a national surveillance programme and the irregular availability of culture for Campylobacter species in clinical and research settings, the true frequency of Campylobacter spp. is still not adequately presented. After taking Trimethoprim for 48 hours, patients' C-reactive protein levels (p=0.0042) and oxygen needs (p<0.021) were significantly lower in the Trimethoprim group than in the Recovery group. The oxygen requirement at Day 2 and Day 5 (p=0.039, p=0.002 respectively) compared to Day 0 was significantly improved in the Trimethoprim group but not in the Recovery group. Death was decreased (17% TMP against 36% for Recovery, p=0.022) although there were no appreciable variations in the need for invasive or non-invasive assistance. Trimethoprim also shortened hospital stays; the average stay was 10 days, compared to 17 days for Recovery (p<0.0032).

Trimethoprim's immunological activities may be the reason for its observed benefits. Among these actions include the inhibition of the Formyl peptide receptors on the surface of circulating neutrophils and monocytes. These receptors play a role in both the neutrophils' release of the "Reactive Oxygen Series," which triggers a cytokine storm, and the phagocytes' homing to the lung in response to inflammatory signals. Trimethoprim's blocking of these receptors will lessen neutrophil activation, soothe the host response, and lessen acute lung injury in Covid-19 cases. According to our findings, oral Trimethoprim lowered hospital stays and death while also reducing fevers, inflammatory indicators, and oxygen requirements more quickly.

Keywords : *Severe COVID-19; ARDS; Trimethoprim; Formyl peptide receptors; Recovery trial*

INTRODUCTION

In 2020–2021, Covid-19 accounted for 66 million cases of adult respiratory distress syndrome globally, making it the most common cause [1]. Many people with the condition recover on their own, but there are few effective treatments available for those who suffer severe respiratory failure [2-4]. According to data, 65–94% of patients hospitalised to critical care for mechanical ventilation died [5, 6]. The UK National Recovery study data demonstrated an 11% reduction in mortality for oxygen-dependent patients taking 6 mg of dexamethasone orally per day [7]. In contrast, there was a rise in mortality during the H1N1 influenza pandemic due to the usage of steroids [8].

Despite extensive research, adult respiratory distress syndrome (ARDS) is a potentially fatal illness with few pharmacological treatments [9, 10]. The lungs are subjected to a prolonged neutrophil assault, which is fueled by the neutrophils' continuous activation through their surface Formyl Peptide Receptors (FPR). One potential therapy strategy is to inhibit these receptors [11,12]. In response to Formyl Peptide Signals (FP) generated by bacteria and injured or dying cells, including mitochondrial DNA, neutrophils migrate to inflamed tissue. These FPs cause neutrophil surface FPRs to become more ac-

tive, releasing oxidants that in turn cause alveolar cell damage and the production of cytokines [13, 14]. Although neutrophils are essential for fighting infection, tissue is poisoned when they infiltrate the lung. ARDS is caused by damage to the capillary endothelium, which results in alveolar oedema, decreased gas exchange, and fibroblast activation [15]. Neutrophils show up early in bronchoalveolar lavage samples from ARDS patients, and their quantity indicates the severity and prognosis of the condition. Acute lung injury is considerably reduced in animal models when neutrophil Formyl peptide receptors are genetically deficient or depleted, indicating a critical function for this receptor [11,16]. Neutrophil NETosis can occur in highly activated and stressed neutrophils that are being driven by an intensifying "cytokine storm." In order to capture pathogens and cell debris, the neutrophil uses this process to extrude its DNA and chromatin into a "NET" (Neutrophil Extracellular Trap).

According to postmortem studies in Covid-19 fatalities, these NETs might cause further tissue damage by blocking blood vessels, which are directly associated to the onset of ARDS and increased mortality [17, 18]. Numerous antibiotics have an impact on the immune system. Through blockade of the neutrophil surface Formyl peptide receptors, studies of the sulphonamide Dapsone (4, 4-diaminodiphenol sulphone) confirm its ability to reduce the generation of both intracellular and extracellular oxygen free radicals as well as proteases released by neutrophils in a dose-dependent manner [19–22]. In the UK, trimethoprim (TMP) is licenced to treat respiratory tract infections. TMP has the same ability to calm the host reaction as Dapsone, Cotrimazole, Cyclosporin, and Hydroxychloroquine by blocking the surface Formyl Peptide receptor on neutrophils [19, 23]. Here, we provide our findings from treating oxygen-dependent patients with severe COVID-19 infection between April 2020 and April 2021 with trimethoprim added to normal therapy, and we compare the results with our patients who gave their agreement to be included in the National UK Recovery study for severe COVID-19.

Method

We have examined information from 130 patients with oxygen-dependent severe Covid-19 infection who were admitted to our ward between April 2020 and April 2021. The UK National Recovery study was open to all patients. These patients were admitted with symptoms for 10–16 days before to admission, including a rising temperature, cough, and dyspnea. They also had a positive Covid swab. On their initial chest X-ray, 85% of patients had bilateral lung infiltrates, and by five days of admission, all patients had radiological alterations. Furthermore, pulmonary emboli were seen in the CT pulmonary angiogram of three individuals. According to the Trust guidelines, patients were started on routine antibiotic therapy, which included oxygen, heparin, and the antibiotics clarithromycin and benzyl penicillin to prevent bacterial super infection. phylaxis pro. One out of every four patients who were enrolled and randomly assigned to the recovery trial received further treatments; the other three patients served as the study's standard therapy comparison arm [24]. Following patient discussion and verbal assent, trimethoprim (TMP) 200 mg 12 hours was added for 5 days in patients who were oxygen dependent and showing obvious signs of clinical deterioration if the Recovery study's requirements were not completed or if the patient denied Recovery enrollment.

Along with the 84 patients who enrolled in the recovery study, the clinical data for 46 TMP-treated patients who did not enter the research are also analysed. Following July 2020, oral dexamethasone (6 mg) was added to regular Covid-19 medication for all patients. We report the results, which include the length of hospital stay, the progression to ventilatory support, the death rate, and the variations in C-reactive protein, body temperature, and oxygen consumption at days 0 through 5. "Day 0" denoted the start of the oral TMP or the day of enrollment in the Recovery trial. Every patient's co-morbidities were noted. Patient Consent and Ethics The data is shown for patients who failed to receive admittance with verbal agreement to the addition of TMP treatment, as well as for those who gave their consent to the Recovery trial. Their anonymised data will be used in this case series with their written agreement.

Analytical Statistics

The group means and standard error of the mean are displayed in the data. Mann Whitney made comparisons between the two patient groups. U test or Chi-square analysis for non-parametric data, as shown in the tables. Between Days 0 and 5, the responses within each group were evaluated using a paired t test. It was significant at $p = <0.05$. PRISM 3.03 and SPSS were the statistical programmes utilised for the analysis. The tables displayed the analytical process.

Results

Case Series

The patient groups and the 130 patients' baseline characteristics are displayed in (Table 1). The two groups' mean ages varied by 5 years, with the Recovery group's mean age of 70 years and a higher proportion of male Caucasian patients. In comparison to the TMP group, the Recovery group had a greater co-morbidity for both hypertension and ischemic heart disease (p=0.022). Drugs for Recovery 1 Study 34 patients were enrolled in the Recovery 1 trial, which ran from April to August 2020. Of these, 26 were randomised to continue receiving normal therapy, 2 to get additional Dexamethasone 6 mg/day, 4 to receive 400 mg/day of Hydroxychloroquine, and 2 to receive 200 mg of Lopinavir + 50 mg of Ritonavir at two tab-lets twice a day. These medications were taken for ten days, or earlier if discharged earlier.

Drug Study 2 Recoveries

Recovery 2 study (September 2020–April 2021) enrolled 50 patients, 35 of whom were randomised to continue receiving conventional therapy. Nine patients were given Aspirin 150 mg/day, two received Colchicine 500 mg twice a day, three received Azithromycin 500 mg/day, and one was given Baricitinib 4 mg twice a day. These medications were taken for ten days, or earlier if the patient was discharged. The results of the recovery research demonstrated that, in oxygen-dependent patients, dexamethasone 6 mg/day reduced death by 11% and baricitinib reduced mortality by 2% in comparison to usual therapy. No additional Recovery trial medications demonstrated any efficacy [7,25].

Outcome

Table 1 shows that 83% of TMP patients were discharged home compared to 64% in the Recovery group (p=0.010), and that 17% of the TMP patient group died (n=8) against 36% in the Recovery group (n=30). This difference was significant (p=0.014). The requirements for high flow nasal oxygen, mechanical ventilation, and continuous positive airway pressure did not differ significantly. For TMP and Recovery group, the average length of hospital stay was 10.6 days and 17.1 days, respectively (p=0.0032) (Table 1). According to the data, adding oral TMP may help patients with severe COVID-19 experience less acute lung injury, which would shorten their hospital stay and lower their death rate as compared to the Recovery group. Nevertheless, these patients were not assigned at random to any group.

TMP blocks the FPR, which may provide protection against worsening acute lung injury even if it has no direct antiviral effects [19]. The advantage of TMP became evident within just 24 hours, most likely as a result of its efficient absorption, which by Day 2 and Day 5 considerably lowered the patients' fever, inflammatory markers, and oxygen requirements—a reduction that the Recovery group of patients did not experience. This medication should lessen the likelihood of neutrophil NETosis and additional lung damage by reducing neutrophil migration to the lung and the release of oxidants and proteases with decreased neutrophil activation [17–19]. Early detection of clinical deterioration is necessary for TMP treatment, since postponing treatment can decrease the drug's effectiveness prior to neutrophil blockage of the alveolar capillary bed. It is challenging to reverse NETosis. Although there are no official ARDS trials for TMP, case reports and circumstantial evidence point to the potential benefits of medications that block the FPR. The literature does, in fact, contain data for rapidly progressive respiratory failure in pulmonary fibrosis and Covid-19 infection, as well as dramatic case reports of rapid recovery from severe ARDS following the addition of intravenous cotrimoxazole (trimethoprim+ sulphamethoxazole) in Middle Eastern Respiratory Syndrome [28, 29]. In animal models, cyclosporin H, a particular FPR inhibitor, lessens acute lung injury when given either before or after the lung insult.

Alveolar protein leak and decreased alveolar neutrophil counts are linked to this medication. Cyclosporin A exhibits comparable effects, such as the capacity to lessen intracellular calcium influx, which is a crucial stage in the start of the NETosis cascade and suggests that FPR plays a functional role in signalling [30]. Targeting individual mediators later in the disease may not be as beneficial as suppressing the "out of control host" via their own neutrophils, as NETosis is a representation of later stages of ARDS.

Conclusion

ARDS is a potentially fatal illness for which there are now no reliable pharmacological treatments. It depicts a picture of a persistent neutrophil onslaught caused by a continuing neutrophil-mediated immunological response. According to research on animals, the neutrophil Formyl Peptide Receptors may play a major role in this illness, and their inhibition may lessen both the immediate lung injury and the host response. Our research, which is corroborated by other data as discussed, demonstrates that oral TMP led to a quicker drop in fevers, inflamma-

tory markers, and oxygen need along with a lower mean hospital stay and mortality. Larger groups of patients with severe Covid19 infections are needed to validate these observations so that the potential to save lives as well as the benefit to mortality and the need for ventilatory support can be properly evaluated.

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