International Journal on Infectious Disease and Epidemiology

Beneficial Effects of Trimethoprim Upon Recovery Time and Survival in Patients with Severe COVID-19

Case Report

Volume 4 Issue 1- 2023

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Article History

Received: January 23, 2023 Accepted: January 31, 2023 Published: January 31, 2023

Abstract

Background: The UK COVID-19 infections in first and second waves were from the alpha and delta variants and seen to be a life-threatening illness for high risk patients mainly from an acute lung injury and acute respiratory distress syndrome. The mainstay of management was supportive, although the use of dexamethasone, remdesivir and even serum from recovered patients was introduced as study data showed beneficial over 2020-2021 if treatment criteria were fulfilled.

Methods: We retrospectively analysed data from 46 patients with oxygen dependent severe COVID-19 who were treated with trimethoprim added to standard therapy antibiotics and compared this to data from 84 patients of comparable severity who entered the Recovery trial during the same time period of April 2020-April 2021.

Results: Patients receiving Trimethoprim showed clinical improvement within 48 hours relative to Recovery patients with reduced C-reactive protein levels ($p=0.0042$) and oxygen requirements ($p<0.021$). The Trimethoprim group showed significant improvements in oxygen requirement at Day 2 and Day 5 ($p=0.039$, $p=0.002$ respectively) relative to day 0 that was not seen for Recovery group. Mortality was reduced (17% TMP versus 36% for Recovery $p=0.022$) without significant differences in the requirement for invasive or non-invasive support. Hospital length of stay was also reduced with Trimethoprim with a mean stay of 10 days versus 17 days for Recovery $p<0.0032$.

Discussion: The benefit seen with trimethoprim may be due to its immunological effects. These effects include blockade of the surface Formyl peptide receptors present on circulating neutrophils and monocytes. These receptors are involved in homing of phagocytes to the lung in response to inflammatory signals and the release of "Reactive Oxygen Series" by the neutrophils driving a cytokine storm. Blocking of these receptors by trimethoprim will reduce neutrophil activation and calm the host response thereby reducing acute lung injury in Covid-19. Our data shows that oral Trimethoprim resulted in a faster reduction in fevers, inflammatory markers and oxygen requirements along with reduced hospital stay and mortality.

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

Abbreviations: ARDS: Adult Respiratory Distress Syndrome; TMP: Trimethoprim; FP: Formyl Peptides; FRP: Formyl Peptide Receptors; ST: Standard Therapy; DNA: Deoxyribonucleic Acid; NETosis: Neutrophil Extracellular Traps; NLR: Neutrophil Lymphocyte Ratio; CRP: Creactive Protein; Fi02: Inspired Fraction of Oxygen; Sp02: Peripheral Oxygen Saturations; CPAP: Continuous Positive Airway Pressure; HFNO: High Flow Nasal Oxygen; ROS: Reactive Oxygen Series

Introduction

Covid-19 became the commonest worldwide cause of adult respiratory distress syndrome in 2020-2021, with 66 million people affected [1]. While the disease is self-limiting for many, for those who develop severe respiratory failure effective treatments were limited [2-4]. Data showed that patients admitted to critical care for Mechanical Ventilation had a mortality of 65-94% [5,6]. The UK National Recovery trial data showed benefit for oxygen dependant patients with oral dexa-

methasone 6mg/day that reduced mortality by 11% [7]. This was in contrast to steroid use in the H1N1 influenza pandemic where mortality was increased [8].

Adult Respiratory Distress Syndrome (ARDS) is a potentially life threatening condition with limited drug therapies despite much research [9,10]. It represents a sustained neutrophil attack upon the lungs, driven by ongoing activation of neutrophils via their own surface Formyl Peptide Receptors (FPR) with blockade of these receptors being a contender for treatment [11,12]. Neutrophils migrate to inflamed tissue in response to released Formyl Peptide Signals (FP) from bacteria and damaged or dying cells including mitochondrial DNA. These FP's stimulate the surface FPR's of neutrophils increasing activation and the release of oxidants that contribute to cytokine release and also alveolar cell injury [13,14]. Neutrophils are critical for responses to infection; however, their infiltration into the lung on mass is toxic to tissue and damages the capillary endothelium, causing alveolar oedema, reduced gas exchange and fibroblast activation all of which is the basis of ARDS [15]. Neutrophils appear early in bronchoalveolar lavage samples from patients with ARDS, and numbers predict severity and mortality. In animal models, depletion of neutrophils or genetic deficiency of the neutrophil Formyl peptide receptors significantly reduces acute lung injury suggesting a key role for this receptor [11,16].

Highly activated and stressed neutrophils driven by an escalating "cytokine storm" can undergo neutrophil NETosis. In this process, the neutrophil extrudes its DNA and chromatin as a 'NET' (Neutrophil Extracellular Trap) to catch infectious agents and cell debris. These NET'S can produce additional tissue damage by blockade of blood vessels that are closely linked to the development of ARDS and increased mortality as reported from postmortem studies in Covid-19 deaths [17,18]. Many antibiotics have effects on immune function. Studies of the sulphonamide Dapsone (4, 4-diaminodiphenol sulphone) confirms its ability to reduce the generation of both intracellular and extracellular oxygen free radicals and proteases release by neutrophils in a dose dependant manner through blockade of the neutrophil surface Formyl peptide receptors [19-22]. Trimethoprim (TMP) is licensed for the treatment of respiratory tract infections in the UK. Like Dapsone, cotrimoxazole, Cyclosporin and hydroxychloroquine, TMP can also block the surface Formyl peptide receptor on neutrophils calming the host response [19,23]. Here we report our observations with trimethoprim added to standard therapy in oxygen dependant patients with severe COVID-19 infection between April 2020-April 2021 and compare outcomes with our patients who consented to entry to the National UK Recovery trial for severe COVID-19.

Method

We have analyzed data from 130 patients admitted to our ward from April 2020-April 2021 who had oxygen dependent severe Covid-19 infection. All patients were offered entry to the UK National Recovery trial. These patients had increasing fever, cough and breathlessness and were Covid swab positive upon admission with symptoms for 10-16 days pre-admission. 85% of patients showed bilateral lung infiltrates on their admitting chest X ray, with radiological changes seen for all patients within 5 days of admission. In addition 3 patients were shown to have pulmonary emboli identified in their CT pulmonary angiogram. Patients were commenced on standard antibiotic therapy as per the Trust guidelines of clarithromycin and benzyl penicillin to protect against bacterial super infection, along with oxygen and heparin prophylaxis. Enrolment and randomization into the recovery trial offered additional treatments for 1 in every 4 patients, with the remaining 3 patients acting as the standard treatment comparison arm of the study [24]. If criteria for the Recovery study were not fulfilled or Recovery entry was declined by the patient, then Trimethoprim (TMP) 200mg 12 hourly was added for 5 days in those who were oxygen dependent with clear signs of clinical deterioration following patient discussion and verbal consent.

The clinical data for 46 TMP-treated patients who did not enter the Recovery study are examined along with 84 patients who enrolled into the recovery study. After July 2020, all patients received oral dexamethasone 6mg added to standard Covid-19 therapy following results from Recovery 1 study findings published in August 2020 [7].

We present the outcomes including mortality, progression to ventilatory support, length of hospital stay and changes in C - reactive protein, body temperature and oxygen requirements at day 0, day 2 and day 5. "Day 0 " indicated the day of entry into the Recovery trial or the commencement of oral TMP. Co-morbidities for all patients were recorded.

Ethics and Patient Consent

The data is presented for those who consented to the Recovery study and for patients who declined or failed entry with verbal consent to the addition on TMP treatment. Written consent has been obtained for their anonymous data to be included in this case series.

Statistical Analysis

The Data is presented shows group means and standard error of the mean. Comparisons between the two groups of patient were by Mann Whitney U test for non-parametric data as indicated on the tables, or Chi-square analysis. Paired t test was used to assess within group responses between Day 0, 2 and 5. Significance was $p = <0.05$. The statistical software used was SPSS and PRISM 3.03 for the analysis. The analysis method was indicated on the tables.

Results

Case Series

The patient groups are shown in (Table 1), with baseline characteristics of the 130 patients. There is a mean 5yrs difference in age between the 2 groups, with the Recovery group having the higher mean age of 70yrs with a higher percentage of male Caucasian patients. Co-morbidity was higher for ischemic heart disease and hypertension in the Recovery group relative to TMP group ($p=0.022$).

Recovery 1 Study Drugs

34 patients entered the Recovery 1 study (April-August 2020) with 26 randomized to ongoing standard care, 2 received added Dexamethasone 6mg/day, 4 randomized to Hydroxychloroquine 400mg/day, 2 randomized to Lopinavir (200mg) with Ritonavir 50mg at 2 tablets twice a day. These drugs continued for 10 days or until discharge if earlier.

Recovery 2 Study Drugs

50 patients were entered Recovery 2 study (Sept 2020-April 2021) with 35 randomized to ongoing standard care, 9 received Aspirin 150mg/day, 2 received Colchicine 500mcg twice a day, 3 received Azithromycin 500mg/day and 1 received Baricitinib 4mg twice a day. These drugs were continued for 10 days or until discharge if earlier. Recovery study findings showed dexamethasone 6mg /day did reduce mortality by 11% in oxygen dependent patients and Baricitinib reduced mortality by 2% relative to standard care. No other Recovery study drugs showed benefit [7,25].

Day 0 Observations

Represents start of the Recovery Study drug treatment allocation or the commencement of oral TMP 200mg BD. The inspired oxygen fraction was significantly higher in the TMP group on Day 0 relative to the recovery group ($p=0.030$). C- reactive protein, body temperature and neutrophil lymphocyte ratio) was comparable across the groups see (Table 2). All patients had Neutrophil to Lymphocyte Ratios (NLR) >7.2, with a NLR ratio >7.3 considered to be adverse and indicating a poorer prognosis [26]. The SpO2/FiO2 ratio (peripheral oxygen saturations ÷ inspired oxygen fraction) correlates with acute lung injury and likely ARDS if values are below 315 in non-ventilated pa-

tients (Table 1). For both patient groups this value was comparable (p=0.134) and <315 and consistent with likely ARDS [27].

At Day 2

Patients with added TMP showed a significant reduction in C-reactive protein (p=0.0042) and oxygen requirements (p=0.021) relative to the Recovery group at day 2. There were no differences in body temperature (p=0.101) or NLR (p=0.620) between the groups. NLR continued to rise in both groups at Day 2 (Table 2). The inspired oxygen fraction (FiO2) in the TMP group was reduced significantly from Day 0 (enrolment) to Day 2 (p=0.039 paired t-test) which was not seen for the Recovery group (p=0.183). TMP patients also showed a significant fall in body temperature (p=0.0001) and C-reactive protein (p=0.0001) but not NLR (p=0.317) from day 0-2. The Recovery patients showed no comparable changes for body temperature, NLR or CRP (p=0.053, p=0.148, p=0.168 respectively paired t-test) see (Table 2).

At Day 5

CRP reduced further in the TMP group relative to Recovery (p=0.0032). Mean Body temperature between the groups was similar at day 5 (p=0.117). Inspired oxygen fraction at day 5 showed no differences between the 2 groups (p=0.091), but had decreased significantly (paired t-test analysis) for the TMP patients at Day 5 relative to day 0 (p=0.0022), along with body temperatures (p=0.0001) and CRP (p=0.0001), this was not seen for the Recovery group. NLR continued to rise for both groups and remained adverse (>11.5) (Table 2). (Figure 1) shows graphical representation of within group data day 0-5 with analysis by paired t-test.

Table 1: Baseline characteristics of patients with severe COVID-19 receiving trimethoprim or Recovery study treatment showing group characteristics and outcomes.

Baseline Characteristics of Patients with Characteristics and Outcomes	TMP + Standard Therapy	Standard Therapy ± Recovery Study	P-value*
Total no of subjects	46	84	
Age, mean (range) +	65 (46-93yr)	70 (34-97)	0.04
Male+	56%	65%	0.51
Percent caucasian+	61%	75%	0.09
CO morbidities %			
Hypertension /Ischaemic heart disease +	30%/13%	37%/28%	0.022
Diabetes Mellitus +	19%	27%	0.397
Chronic obstructive pulmonary disease +	18%	23%	0.482
Duration of symptoms pre-admission+ (days)	10.67±2.4	16.5±1.54	0.0051
Chest X ray showing bilateral interstitial infiltrates on admission (%) +	93%	77%	0.042
SPO2 ÷ FIO2 on admission (values <315 indicate acute lung injury) +	268±16	302± 13	0.134
Outcome data	**TMP + standard therapy**	**Standard therapy ± Recovery**	
Died +	8 (17%)	30 (36%)	0.014
*CPAP/HFNO +	8 (17%)	10 (12%)	1.01
Mechanical ventilation +	2 (4%)	6 (7%)	0.9
Discharged +	38 (83%)	54(64%)	0.01
Total length of stay days +	10.67±0.9	17.15±1.49	0.0032

*Continuous Positive Airway Pressure (CPAP)/ High Flow Nasal Oxygen (HFNO), Chi Square test +.

Table 2: Observed Changes for TMP and Recovery groups on Day 0, 2 and 5 including between group and intra-group analysis of changes in oxygen requirement, fevers, CRP and Neutrophil Lymphocyte Ratio (NLR).

Data	Mean± SEM+	Mean± SEM+	Mann Whitney U Test
Day O data (start of treatment)	**TMP + standard therapy**	**Standard therapy ± Recovery**	**TMP Versus Recovery p-value***
Fraction of inspired oxygen (FiO2)	0.41±0.17	0.35±0.10	0.03
Body temperature (°C)	37.6±0.12	37.7±0.09	0.29
C-Reactive Protein (mg/L)	111±12.3	104±9.0	0.64

Neutrophil Lymphocyte Ratio (NLR)	7.25±1.1	9.15±1.1	0.279
Day 2 admission data			
Fraction of Inspired Oxygen (FiO2)	0.33±17.3	0.38±23.1	0.021
Body temperature (°C)	37.1±0.12	37.3±0.08	0.101
C-Reactive Protein (mg/L)	66.5±9.9	114.4±10.6	0.0042
Neutrophil Lymphocyte Ratio (NLR)	10.3±1.3	12.77±1.4	0.62
Day 5 admission data			
Fraction of inspired oxygen (FiO2)	0.31±16.3	0.38±22.7	0.091
Body temperature (°C)	36.9±0.10	37.2±0.08	0.117
C-Reactive Protein (mg/L)	49±8.1	96±9.6	0.0032
Neutrophil Lymphocyte Ratio (NLR)	13.1±3.1	11.5±1.3	0.646
Analysis of Day 0 versus Day 2 data by paired t-test for individual groups	**TMP group p-value**	**Recovery Group p-value**	**Comments**
Change in Fraction of Inspired Oxygen (FiO2)	0.039	0.183	Reduced TMP group only
Change in Body temperature (°C)	0.0001	0.0533	Reduced TMP group only
Change in C-Reactive Protein (mg/L)	0.0001	0.1689	Reduced TMP group only
Change in Neutrophil Lymphocyte Ratio (NLR)	0.317	0.148	No changes
Analysis of Day 0 versus Day 5 data by paired t-test for individual groups	**TMP group p-value**	**Recovery Group p-value**	**Comments**
Change in Fraction of Inspired Oxygen (FiO2)	0.0022	0.217	Reduced TMP group only
Change in Body temperature (°C)	0.0001	0.55	Reduced TMP group only
Change in C-Reactive Protein (mg/L)	0.0001	0.281	Reduced TMP group only
Change in Neutrophil Lymphocyte Ratio (NLR)	0.575	0.06	No changes

+ SEM (standard error of the mean).

Outcome

17% of the TMP patient group died (n=8) versus 36% in Recovery group (n=30) and this difference was significant (p=0.014), with 83% of TMP patients discharged home versus 64% in the Recovery group (p=0.010) (Table 1). There were no significant differences in the requirement for Continuous Positive Airway Pressure, high flow nasal oxygen or mechanical ventilation. The mean length of hospital stay was 10.6 days for TMP and 17.1 days for Recovery group (p=0.0032) (Table 1).

Discussion

The Data presented suggests that the addition of oral TMP may reduce acute lung injury in patients with severe COVID-19, thereby reducing hospital length of stay and mortality relative to that seen for the Recovery group. These patients however, were not randomized to each group. Although TMP has no direct anti-viral effects it probably offers protection against escalating acute lung injury via blockade of the FPR [19]. The benefit of TMP was apparent within 24 hours, likely reflecting its excellent absorption resulting in significantly reduced fever, inflammatory markers and oxygen requirements by Day 2 and Day 5 that was not seen for the Recovery group of patients. This drug should reduce neutrophil migration to the lung and the release of oxidants and proteases with reduced neutrophil activation lowering the risk of neutrophil NETosis and further lung injury [17-19].

Treatment with TMP would require timely recognition of clinical deterioration, as delayed treatment would reduce the ability of this drug to act before blockade of the alveolar capillary bed by neutrophil NETosis is difficult to reverse. In the absence of formal ARDS trials of TMP there is circumstantial data and case reports suggesting that drugs blocking the FPR have benefit. Certainly the literature contains dramatic case reports of rapid recovery from severe ARDS following the addition of intravenous cotrimoxazole (trimethoprim+ sulphamethoxazole) in Middle Eastern Respiratory Syndrome, and data for rapidly progressive respiratory failure in pulmonary fibrosis and Covid-19 infection [28,29]. Cyclosporin H, a specific inhibitor of the FPR, reduces acute lung injury in animal models if administered

before or after the lung insult. This drug is associated with reduced alveolar neutrophil numbers and alveolar protein leak. Cyclosporin A shows similar effects, including the ability to reduce intracellular calcium influx that is a key step in the initiation of the NETosis cascade and indicates a functional role for FPR signally [30]. Since NETosis represents later stages of ARDS, dampening the "out of control host" via their own neutrophils may have greater benefit than targeting individual mediators later in the disease.

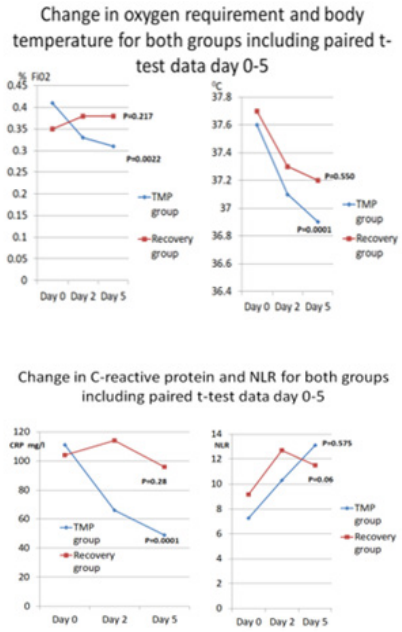

Figure 1: Mean Changes within each group for oxygen requirement, C-reactive protein, body temperature and Neutrophil Lymphocyte Ratio (NLR) shown as mean values with p value (paired t-test) for Day 0 to Day 5 values for each group.

Quadery and colleagues performed an analysis of 111 patients with severe Covid-19 who were openly randomized to cotrimoxazole (trimethoprim+ sulphamethoxazole) or optimal standard therapy that included broad spectrum antibiotics with dexamethasone, 6mg/day along with remdesivir and heparin prophylaxis [31]. Entry criteria included an oxygen requirement of 10-15 litres/min. The patient's were randomized 1:1 to optimal standard therapy (n=55) or optimal standard therapy with oral cotrimoxazole (n=56) for 7 days (dose 960mg 8hrly). The results show 2 well matched groups (mean age 52yrs) with in-hospital mortality of 11% with added cotrimoxazole versus 29% without. The significant reduction in mortality was the primary outcome (p=0.020) [32]. A reported case series from India (West Bengal 2020) also examined the outcome in 50 critical Covid-19 patients given Standard Therapy (ST) compared to 151 patients treated with ST and added cotrimoxazole 960mg TDS. The mortality was 40% in the ST only group and 13% with cotrimoxazole and ST. There were differences in the requirement for mechanical ventilation, being 40% for ST versus 15% for added cotrimoxazole [33].

Both Trimethoprim and Cotrimoxazole are inexpensive drugs licensed for use in respiratory infections and are available worldwide and may have benefit in preventing acute lung injury in this pandemic. A published case series of outpatient management of acute Covid-19 infection with home oxygen treatment and oral cotrimoxazole prevented hospital admission in 14 out of 15 cases. The admitted case was due to coexistent dysentery that required treatment [34]. The low cost of TMP or cotrimoxazole makes it an affordable drug for many poorer countries to reduce admissions and mortality as suggested by this various data [35]. In the UK, 2.23 million doses of Molnupiravir (a costly anti-viral drug) for Covid-19 has been purchased for outpatient use. Sadly data shows no benefit over placebo in reducing hospital admission and mortality despite early data suggesting a 50% reduction that was not substantiated with further data in the panoramic trial [36].

Conclusion

ARDS is a potentially life threatening condition with no effective drug therapies to date. It represents a picture of a sustained neutrophil attack driven by ongoing immune activation involving neutrophils. Animal studies suggest that the neutrophil Formyl Peptide Receptors have significant involvement in this condition and blockade may reduce the host response and acute lung injury. Our data shows that oral TMP resulted in a faster reduction in fevers, inflammatory markers and oxygen requirement with reduced mean hospital stay and mortality, which is supported from other data as discussed. These observations require confirmation in larger groups of patients with severe Covid19 infections, so benefit to mortality and the need for ventilatory support may be fully assessed along with the potential to save many thousands of lives worldwide.

Funding

No funding was involved in this case series.

Acknowledgement

None.

Conflict of Interest

The authors declare no conflict of interests.

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