Improved outcomes with Trimethoprim or Cotrimoxazole in patients with severe COVID-19: A District Hospital experience

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Abstract

Background

COVID-19 may become life-threatening as a result of the host mediated cytokine storm syndrome. There is no proven effective treatment available and the mainstay of management is supportive.

Methods

We retrospectively analysed data from 22 patients with severe COVID-19 treated with oral Trimethoprim (TMP) or Cotrimoxazole (CTX) in addition to standard therapy (ST) and compared these with 22 patients with severe COVID-19 who had received ST alone.

Results

We observed that patients with severe COVID-19 receiving TMP/CTX in addition to ST had better outcomes. These include reduction in mortality (5% versus 32%, p=0.022), need for ventilatory support (3 versus 16 patients, p<0.001) and length of hospital stay (mean: 9 versus 22 days, p<0.001). Clinical parameters improved within 48 hours of starting treatment with TMP/CTX (SpO_2/FiO_2, p<0.001; C-Reactive Protein, p=0.002).

Discussion

These results may be due to the antimicrobial and anti-inflammatory effects of TMP/CTX. Clinical trials with CTX in patients with severe COVID-19 are ongoing.

Background

The Coronavirus Disease (COVID-19) pandemic has affected over 16.7 million people resulting in more than 661,000 deaths.[1] While the disease is self-limiting for the majority, for those with severe disease no effective treatment exists.[2] Risk factors for severe disease include male sex, obesity, ethnicity and diabetes alongside prior cardiac or respiratory diseases.[3]

A subgroup of patients with severe COVID-19 have unremitting fevers, blood cytopenia and 50% may develop pulmonary involvement associated with the overproduction of cytokines (soluble inflammatory immune mediators) generated by an increased host immune response to the virus.[4] This 'cytokine storm' involves interleukin 1, 2 and 6, with interferon-γ and tumour necrosis factor-α. Together these cytokines lead to T- lymphocyte, monocyte and neutrophil activation.[5] Respiratory failure and acute respiratory distress syndrome (ARDS) are the most serious complications of pulmonary involvement for which the mainstay of treatment is oxygen therapy. Some patients require non-invasive or invasive ventilatory support and have a higher mortality.[6] In addition, secondary bacterial infections are often seen in patients with viral pneumonias. *Staphylococcus aureus* being the commonest organism in Influenza A, carries a poor prognosis. MRSA and *Sternotrophomonous maltophilia* are more commonly seen in ventilated patients with SARS.[7,8]

Cotrimoxazole (a combination of Trimethoprim and Sulphamethoxazole) is an anti-folate bactericidal antibiotic indicated for the treatment of hospital acquired pneumonia in the UK.[9,10] It is effective against a number of microorganisms including Methicillin sensitive *Staphylococcus aureus* (MSSA), Methicillin resistant *Staphylococcus aureus* (MRSA), *Klebsiella pneumoniae*, *Haemophilus influenzae B* and *Stenotrophomonas maltophilia*.[11]

Trimethoprim is licensed for the treatment of respiratory tract infections in the UK and has comparable efficacy and a better safety profile than Cotrimoxazole.[12,13] In addition to their antimicrobial effects, Trimethoprim and Cotrimoxazole may have anti-inflammatory effects.[14]

There is also a case report describing clinical recovery from ARDS in a patient with MERS after the use of Cotrimoxazole.[15]

Here we report our experience with Trimethoprim and Cotrimoxazole in addition to standard therapy in patients with severe COVID-19 compared with retrospective data from a group of patients with confirmed severe COVID-19 receiving standard therapy alone.

Methods

We retrospectively analyzed data obtained from electronic case records of patients admitted to two district hospitals in the UK from 17 March 2020 to 18 April 2020. These patients were not eligible for the national Recovery Trial at the time of initiation of Cotrimoxazole or Trimethoprim. Data was collected, anonymized and stored in a secure and encrypted web-based portal.

Patients admitted with increasing fever, cough and breathlessness were commenced on standard therapy antibiotics of Clarithromycin and Benzyl Penicillin for possible super infection secondary to COVID-19 as per local guidelines. Chest-X-rays and/or CT chest scans confirmed lung infiltrates in a pattern consistent with a radiological diagnosis of COVID-19. All patients met the WHO criteria for severe COVID-19 (COVID-19 + Oxygen saturations < 90% on room air at rest).[16]

Cotrimoxazole and Trimethoprim are indicated in the UK for the treatment of pneumonia and respiratory tract infections respectively. Patients demonstrating a poor initial response to standard therapy and considered to be at risk of further deterioration because of increasing fevers and oxygen requirements were given either oral Cotrimoxazole (160mg of trimethoprim and 800mg sulphamethoxazole) 12hrly (n=4) or oral Trimethoprim (200 mg) 12 hrly (n=18).[9,12]

Patients were given Cotrimoxazole or Trimethoprim after they had been fully informed of their condition and the risk of further deterioration. It was explained that the treatment was in addition to the standard therapy they were already receiving. Cotrimoxazole and Trimethoprim were considered to be safe drugs for these patients and were used in what was considered to be their

best interests. The aim was to reduce the mortality from severe ARDS in patients with potentially life-threatening COVID-19 at a time when no proven treatment was available. Inclusion into a trial was not possible at that time. This was in accordance to the national and international guidelines of good medical practice and research ethics.[17,18]

Clinical data of 22 patients with severe COVID-19 on Trimethoprim or Cotrimoxazole in addition to standard therapy was retrospectively analysed. Of these patients 68% (n=15) subsequently tested positive by RT-PCR.

Historic data from a further 22 patients with confirmed COVID-19 with comparable age and disease severity receiving standard therapy are also presented.

Mortality, progression to ventilatory support, length of hospital stay and changes in oxygen requirements, respiratory rate, body temperature and C-Reactive Protein were compared between the two groups.

'Day 0' is the time of initiation of Trimethoprim or Cotrimoxazole. In those receiving standard therapy alone, it was the day that disease severity (oxygen requirement) matched the mean oxygen requirement of those receiving Trimethoprim or Cotrimoxazole.

Data on comorbidities previously suggested to be linked to higher risk of mortality in COVID-19 were also compared between the two groups.

Ethical considerations

As per the prevailing regulation pertaining to the pandemic period, ethical clearance was not required for the entry, storage, processing and dissemination of anonymised clinical data for research purposes. In addition, patient consent for publication of this clinical data for research purposes has been waived.[17]

Statistical Analysis

Continuous data is presented using means and standard deviations. Comparisons between two groups of continuous data were made using the t-test for parametric and Mann Whitney U test/Wilcoxon signed rank test for non-parametric data.

Categorical data is presented as number or percentage of patients. For categorical variables comparisons between two groups were done using Chi-squared test or Fishers exact test (for small numbers). Survival was assessed by the Kaplan–Meier method. Comparisons between two groups were performed using the log-rank test. A p-value of < 0.05 was considered to be significant. The statistical software SPSS version 25 was used for the analysis.

Results

Baseline characteristics from anonymized record reviews are shown (table 1) for standard therapy patients and those treated with the addition of Trimethoprim or Cotrimoxazole to standard therapy. At 'Day 0' these patients had experienced symptoms for a median of 10 days in the group receiving Trimethoprim or Cotrimoxazole and 8 days in the standard therapy group.

The groups were comparable for age, sex, ethnic group, diabetes, chronic lung disease, ischemic heart disease and chronic kidney disease. Hypertension was lower in the group receiving Trimethoprim or Cotrimoxazole (14%) compared with standard therapy alone (50%).

Baseline observations were similar for oxygen requirements (FiO_2), respiratory rate, C-Reactive Protein, body temperature and lung infiltrates (table 1). All patients had neutrophil to lymphocyte ratios (NLR) >7.3. An NLR ratio >3.3 has been shown to imply a poorer prognosis.[19]

The SpO_2/FiO_2 ratio (peripheral oxygen saturations ÷ inspired oxygen) correlates with acute lung injury, with ARDS being associated with a ratio below 315 in non-ventilated patients. For both patient groups this ratio was <250, confirming the clinical impression of ARDS.[20]

At 48hrs (table 2) patients receiving Trimethoprim or Cotrimoxazole showed a significant reduction in fevers, C-Reactive Protein, respiratory rate and oxygen requirements (FiO_2). The SpO_2/FiO_2 ratio, which marks acute lung injury, had also improved to a mean of 320 that was consistent with reduced injury. The standard therapy patients showed no overall changes in any parameters (table 2).

Figure 1 shows mean values with standard deviations and 95% confidence intervals from 'Day 0' to 'Day 5' for oxygen requirement (FiO_2), SpO_2/FiO_2 ratio, body temperature and C- reactive protein. This demonstrated continuing improvement for patients receiving Trimethoprim or Cotrimoxazole in addition to standard therapy.

21 out of 22 patients who received Trimethoprim or Cotrimoxazole were discharged well without oxygen after a mean stay of 9 days (table 2). There was one death due to ARDS (4.5%) while on the second day of mechanical ventilation in the intensive care unit.

Data from the patients receiving standard therapy alone, showed that 7 patients died (32%) from ARDS with a median time to death of 7 days (IQR range 5-20 days) from admission. The mean length of hospital stay for surviving patients was 22 days.

Figure 2 shows the Kaplan Meier estimates of survival from date of admission in patients who received Trimethoprim or Cotrimoxazole versus standard therapy alone.

Discussion

Our data suggest that the addition of oral Trimethoprim or Cotrimoxazole reduces acute lung injury in patients with severe COVID-19, thereby reducing the need for ventilatory support and improving outcomes.These drugs have no direct anti-viral effects but may offer protection against ARDS by their antimicrobial, anti-inflammatory and immunomodulatory effects.[21,22,23] The beneficial effects of Trimethoprim and Cotrimoxazole were apparent within hours of the first dose, likely reflecting their excellent absorption and lung penetration.[24]

ARDS is one of the life-threatening complications of COVID-19 caused by the body's hyper-immune response to the virus in the form of a cytokine storm syndrome (CSS).[25] The CSS occurs as a result of neutrophil recruitment into the lung due to the stimulation of the formyl peptide receptors (FPRs) by Damage Associated Molecular Patterns (DAMPs) which are released upon mitochondrial injury of host cells. FPRs are situated on the outer surface of the cell membrane of the neutrophils and monocytes, and when stimulated cause the release of intracellular and extracellular reactive oxygen series (ROS) which can drive the cytokine activation and stimulate the formation of Neutrophil Extracellular Traps (NETs) which block the alveolar capillary bed leading to hypoxaemia.[26,27]

Cotrimoxazole blocks the FPR's and can reduce the movement of neutrophils to the lung, generation of ROS, production of pro-inflammatory cytokines and formation of NETs.[14,23,24,28,29,30,31,32] Published data shows that cotrimoxazole has anti-cytokine effects reducing interleukin-1, 2, 6,8 and tumour necrosis factor-α production.[33,34,35,36,37,38,39] Several of these cytokines are shown to be raised in the cytokine storm associated with COVID-19.[19] This offers a possible explanation for the observed clinical benefit by reducing neutrophil, monocyte and lymphocyte activation leading to a reduction in the risk of ARDS.[33,34,35,36] Timely recognition of any clinical deterioration from the underlying cytokine storm syndrome is important. Delayed treatment, may reduce the ability of these drugs to act before blockade of the alveolar capillary bed by neutrophils occurs, with the risk of profound hypoxemia that may be difficult to reverse.[27]

Trimethoprim and Cotrimoxazole are inexpensive drugs indicated for use in respiratory infections with excellent efficacy and few serious side effects.[9,12,40] They are available worldwide and may have benefit in preventing acute lung injury in this pandemic.[40]

Cotrimoxazole may have advantages over Trimethoprim due to the additional antimicrobial and possible anti-inflammatory effects of Sulphamethoxazole along with an intravenous preparation for use in deteriorating patients.[14,24]

Given the probable effectiveness of the said treatment ethical considerations necessitate the dissemination of this information to the wider scientific community for further research.[41] A randomized control trial with Cotrimoxazole in patients with severe COVID-19 is currently underway (ClinicalTrials.gov Identifier NCT04470531) and results are awaited.[42]

Limitations

Given that this is a retrospective analysis of clinical data there is risk of selection bias. There can be potential confounders that have not been accounted for such as malignancy and obesity, which have subsequently been shown to be associated with poor prognosis. Although hypertension is obviously not matched between the two groups, recent studies have not shown hypertension to be an independent risk factor for developing severe disease or mortality in patients with COVID-19.[43] Trimethoprim and Cotrimoxazole were administered orally 3 days after admission. Administration at the time of diagnosis of severe COVID-19 and through the intravenous route could potentially have some added benefit.

Conclusion

If the results from the ongoing randomized control trial confirm the beneficial effects of Cotrimoxazole in patients with severe COVID-19 then we will be able to reduce the need for hospital beds and oxygen therapy especially when supply is limited, and thus potentially save thousands of lives worldwide.

Table 1: Baseline characteristics of patients with severe COVID-19 receiving Trimethoprim (TMP) or Cotrimoxazole (CTX) with standard therapy versus standard therapy alone

	TMP/CTX + standard therapy	Standard therapy alone	p-value*
Subjects	22	22	
Age, mean (± SD[+])	59 (±15)	60 (±12)	0.760
Male	59%	68%	0.531
Ethnicity			
Asian	23%	14%	0.615
Afro-Caribbean	9%	9%	
Mixed	13%	5%	
Caucasian	55%	72%	
Comorbidities			
Hypertension	14%	50%	0.010
Diabetes Mellitus	18%	27%	0.472
Ischemic Heart Disease	9%	14%	0.635
Chronic obstructive pulmonary disease	23%	9%	0.412
Chronic kidney disease > 2	9%	23%	0.412
Baseline observations: Day 0			
Clinical parameters	mean ± SD	mean ± SD	
Days from admission to Day 0	3 ± 3	1 ± 3	0.180
Fraction of inspired oxygen (FiO_2)	0.45 ± 0.17	0.44 ± 0.10	0.760
Oxygen saturation/fraction of inspired oxygen (SpO_2/FiO_2) ratio	244 ± 97	220 ± 49	0.690
Respiratory rate (breaths/min)	24 ± 9	21 ± 5	0.952
Body temperature (°C)	37.6 ± 0.8	37.8 ± 1	0.638
C-Reactive Protein (mg/L)	120 ± 74	148 ± 74	0.307
Neutrophil Lymphocyte ratio (NLR)	7.8 ± 9.8	7.4 ± 2.4	0.029
% of subjects with infiltrates on the Chest X-Ray	91%	100%	0.488

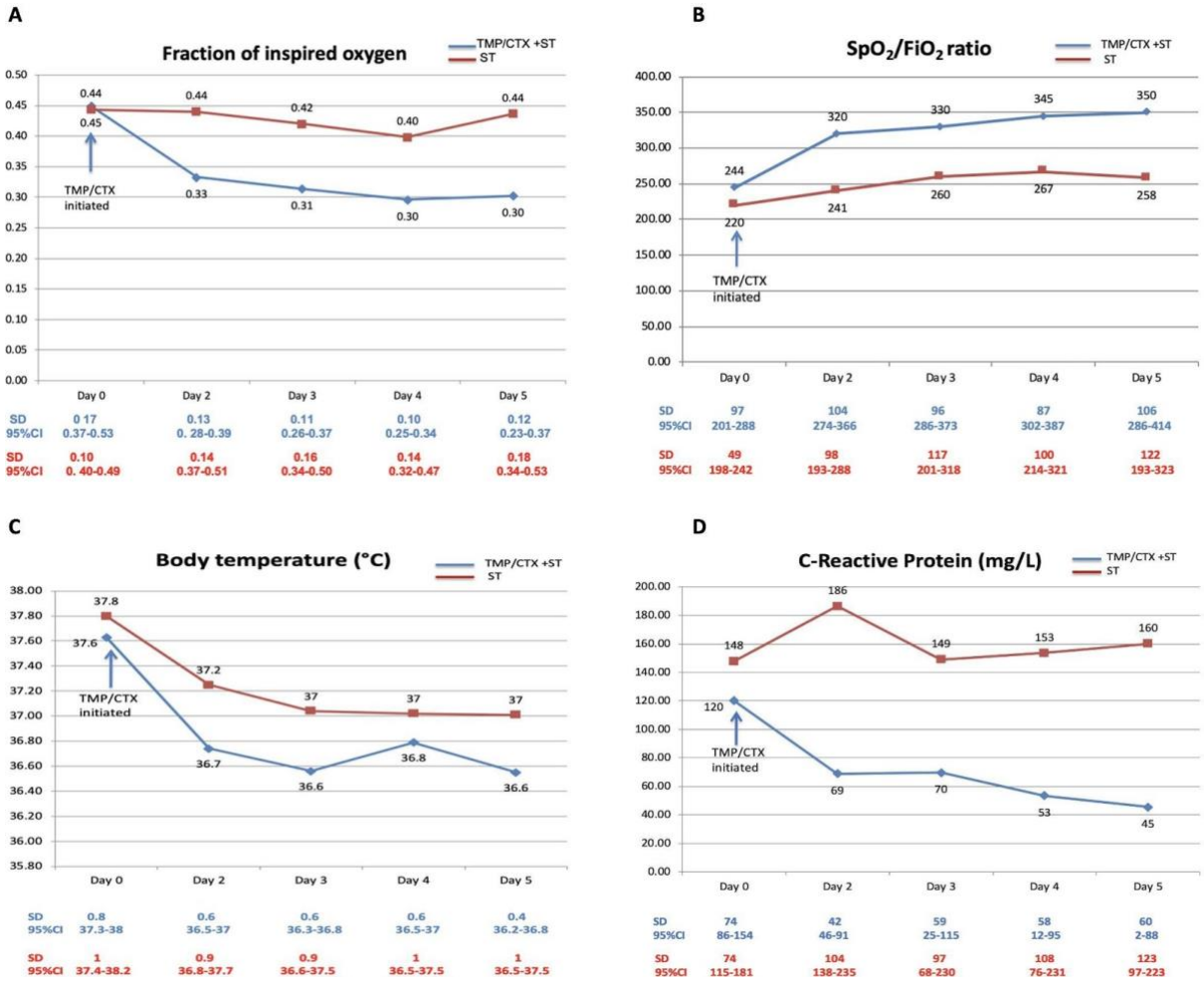
*Comparison between continuous variables and categorical variables was made by the Mann-Whitney U test and Chi Square test /Fishers exact test respectively. A p-value of <0.05 was considered statistically significant.
+SD= Standard Deviation

Table 2: Primary outcomes and observations on day 0 and day 2 in patients with severe COVID-19 receiving Trimethoprim (TMP) or Cotrimoxazole (CTX) with standard therapy versus standard therapy alone

Primary Outcomes			
Outcome measures, number of cases (%)	**TMP/CTX + standard therapy**	**Standard therapy alone**	**p-value***
Discharged	21 (95.5%)	15 (68%)	-
Died	1 (4.5%)	7 (32%)	0.046
Ventilatory support	3 (14%)	16 (73%)	<0.001
Continuous positive airway pressure	2 (9%)	11 (50%)	0.001
Mechanical ventilation	1 (5%)	5 (23%)	0.185
Length of stay in days, (mean ± SD$^+$)	9 (± 4)	22 (± 13)	<0.001
Observations on Day 0 and Day 2: TMP/CTX + standard therapy (number of cases = 22)			
	mean ± SD$^+$	mean ± SD$^+$	
Clinical parameters	**Day 0**	**Day 2**	**p-value**
Fraction of inspired oxygen (FiO_2)	0.45 ± 0.17	0.33 ± 0.13	0.001
Oxygen saturation/fraction of inspired oxygen (SpO_2/FiO_2) ratio	244 ± 97	320 ± 104	<0.001
Respiratory rate (breaths/min)	24 ± 9	20 ± 2	0.035
Body temperature (°C)	37.6 ± 0.8	36.7 ± 0.6	0.001
C-Reactive Protein (mg/L)	120 ± 74	69 ± 42	0.002
Observations on Day 0 and Day 2: Standard therapy alone (number of cases = 22)			
	mean ± SD$^+$	mean ± SD$^+$	
Clinical parameters	**Day 0**	**Day 2**	**p-value**
Fraction of inspired oxygen (FiO_2)	0.44 ± 0.10	0.44 ± 0.14	0.864
Oxygen saturation/fraction of inspired oxygen (SpO_2/FiO_2) ratio	220 ± 49	241 ± 98	0.286
Respiratory rate (breaths/min)	21 ± 5	21 ± 5	0.965
Body temperature (°C)	37.8 ± 1	37.2 ± 0.9	0.097
C-Reactive Protein (mg/L)	148 ± 74	186 ±104	0.040

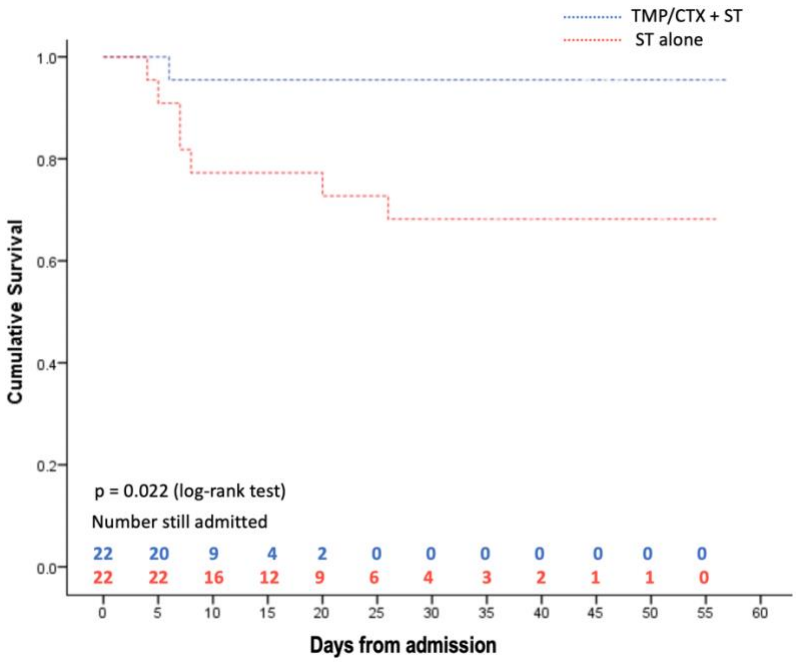
*Comparison between continuous and categorical variables was made by using Wilcoxon Signed Ranks test (for clinical parameters) / Mann-Whitney U test (for length of stay) and Chi Square test /Fishers exact test respectively. A p-value of <0.05 was considered statistically significant. $^+$SD = standard deviation

Figure 1: Observations between Day 0 and Day 5 in patients with severe COVID-19 receiving Trimethoprim (TMP) or Co-trimoxazole (CTX) with standard therapy (ST) or ST alone: A) Fraction of inspired oxygen (FiO_2), B) SpO_2 /FiO_2 ratio, C) Body temperature and D) C-Reactive Protein



Definition of abbreviations:
SpO2 = peripheral capillary oxygen saturation; SD = standard deviation; 95% CI = 95% confidence interval;
Data are presented as mean ±S D and 95% CI

Figure 2: Kaplan-Meier estimates of survival from date of admission comparing outcomes in patients with severe COVID-19 receiving Trimethoprim (TMP) or Cotrimoxazole (CTX) with standard therapy (ST) or ST alone



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