The beneficial effects of oral trimethoprim or cotrimoxazole in patients with severe COVID-19: A case series

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Abstract

COVID-19 may become a critical illness which is thought to be mediated by a cytokine storm syndrome. There is no effective anti-viral treatment to date and the mainstay of treatment is supportive. We treated 22 patients with severe COVID-19 with oral trimethoprim (TMP) or cotrimoxazole (CTX) in addition to standard antibiotic therapy (ST) and compared this with 22 patients with severe COVID-19 receiving standard therapy alone. We observed that the patients with severe COVID-19 receiving TMP/CTX in addition to ST had significantly better outcomes including reduced in-patient mortality (5% versus 32%), length of hospital stay (mean, 9 versus 22 days), and the need for ventilatory support (numbers, 3 versus 16) with improved clinical parameters within 48 hours of starting treatment. This may be due to the anti-cytokine effects of TMP/CTX. Urgent clinical trials are recommended.

The Coronavirus Disease (COVID-19) pandemic carries an estimated mortality of 3.7-4.3% compared with <1% for influenza and no proven treatment yet exists.[1] Risk factors for more severe disease include male sex, obesity, ethnicity, hypertension and diabetes alongside prior cardiac or respiratory diseases.[2]

A subgroup of patients with severe COVID-19 have unremitting fevers, blood cytopenia's and 50% may develop pulmonary involvement associated with the over-production of cytokines (soluble inflammatory immune mediators) generated by an increased immune response to the virus.[3] 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.[4] Respiratory failure and acute respiratory distress syndrome (ARDS) are one of the most serious complications of pulmonary involvement with the mainstay of treatment being oxygen therapy. Some patients require non-invasive or invasive ventilatory support which is associated with higher mortality and possible multi-organ failure.[5]

Although not universally recognized, the sulphonamide antibiotics dapsone (4, 4-diaminodiphenolsulphone) and cotrimoxazole (a combination of trimethoprim-sulphamethoxazole) have effects upon the immune system which were first described for dapsone over 50 years ago. Both drugs share the same sulphonamide ring with similar antibacterial effects, with detailed studies of dapsone showing a dose-dependent reduction in the generation of tissue damaging 'oxygen free radicals' from neutrophils.[6,7] This reduction results from dapsone's ability to block stimulation of the formyl peptide receptors (FPR), which are abundantly expressed on the surface of neutrophils and monocytes. Their activation drives the production of both intracellular and extracellular

oxygen free radical release leading to further inflammatory cytokine production.[6,8] The blockade of FPR by dapsone therefore has marked anti-inflammatory effects. Similar data exists for cotrimoxazole and trimethoprim.[9,10]

From the medical literature there are scattered case reports describing clinical recovery from acute respiratory distress syndrome after the addition of cotrimoxazole, and here we report our experience with the use of trimethoprim and cotrimoxazole in the treatment of severe COVID-19.[11,12]

All patients admitted with increasing fever, cough and breathlessness commenced standard therapy antibiotics of clarithromycin and benzyl penicillin for possible super infection secondary to COVID-19. These patients had been self-isolating for 7-10 days but had become increasing unwell leading to hospital admission. Their chest-X-ray's or CT chest scans confirmed lung infiltrates in a pattern consistent with a radiological diagnosis of COVID-19.

Since both cotrimoxazole and trimethoprim are licensed in the UK for the treatment of respiratory infections and pneumonia, we gave a 5-day course as best practice to patients demonstrating an acute hyper-inflammatory response (cytokine storm syndrome) with increasing fevers and oxygen requirements, who were considered to be at risk of further deterioration. These 22 patients commenced oral trimethoprim (TMP) 200mg 12hrly (18 cases) or cotrimoxazole (CTX) 960mg 12hrly (4 cases); the latter containing 160mg of trimethoprim and 800mg sulphamethoxazole, in addition to standard antibiotic therapy. All patients fitted the WHO criteria for severe COVID-19.[12] Historic data from record reviews of a further 22 patients with severe COVID-19 receiving standard therapy are also presented.

Baseline characteristics from anonymized record reviews are shown in table 1 for standard therapy patients and those treated with the addition of TMP or CTX to standard therapy. 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 TMP/CTX added group at 14% compared with standard therapy alone at 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 is documented to imply a poorer prognosis.[13]

The SpO_2/FiO_2 ratio (peripheral oxygen saturations ÷ by 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.[12,14]

At 48hrs (table 2) patients with added TMP or CTX showed a significant reduction in fevers, C-reactive protein, respiratory rate and oxygen requirements (FiO_2). The $SpO2/FiO_2$ 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 deviation and 95% confidence intervals from day 0 to day 5 for oxygen requirement (FiO_2), $SpO2/FiO_2$ ratio, body temperature and C-reactive protein. This demonstrated continuing improvement for the added TMP/CTX patients.

21 out of 22 patients with added TMP or CTX were discharged well without oxygen after a mean stay of 9 days (table 2). There was 1 death due to ARDS (4.5%) during 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). The mean length of hospital stay for surviving patients was 22 days; although 1 patient still remains in hospital. The standard therapy group required a total of 65 intensive care bed days versus 1 day for the TMP/CTX group.

Figure 2 shows the Kaplan Meier plot for survival versus days from admission for the standard therapy (ST) and TMP/CTX with ST group.

Data presented from our first 22 cases, suggests that the addition of oral TMP or CTX 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. The beneficial effects of TMP/CTX were apparent within hours of the first dose, likely reflecting their excellent absorption and lung penetration.

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.[15]

Published data shows that cotrimoxazole has anti-cytokine effects reducing interleukin-1, 2, 6, 7, 8 and tumour necrosis factor-α production. Several of these cytokines are involved in the cytokine storm of COVID-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.[16-20]

Trimethoprim or cotrimoxazole are inexpensive drugs licensed for use in respiratory infections with few serious side effects. They are generally available worldwide, and may have benefit in preventing acute lung injury in this pandemic. Cotrimoxazole may have advantages over trimethoprim due to the additional immune effects of sulphamethoxazole along with an intravenous preparation for use in deteriorating patients.

Reducing ARDS and oxygen demand may be vital to saving lives in countries where healthcare may be easily overwhelmed. We recommend that these observations should be tested in clinical trials of TMP or CTX in the management of severe COVID-19.

Table 1: Baseline characteristics of patients with severe COVID-19 receiving trimethoprim (TMP)/cotrimoxazole (CTX) with standard therapy or 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	
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

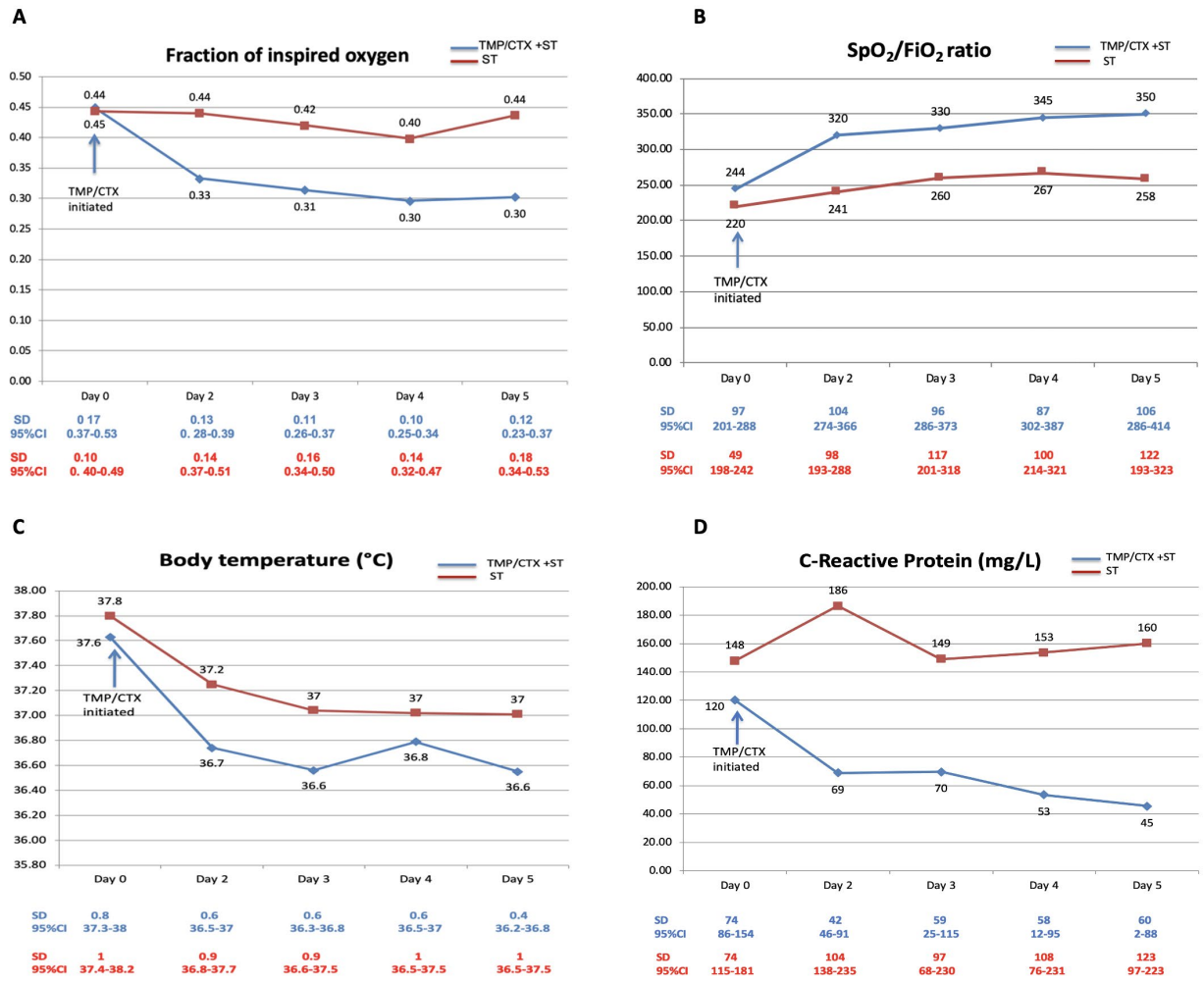
*Comparison between continuous variables and categorical variables was made by the Mann-Whitney U test and Chi Square test /Fishers exact test respectively. A p-value of <0.05 was considered statistically significant.
[+]SD= Standard Deviation

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

Primary Outcomes			
Outcome measures, number of cases (%)	**TMP/CTX + standard therapy**	**Standard therapy alone**	**p-value***
Discharged	21 (95%)	14 (64%)	0.416
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

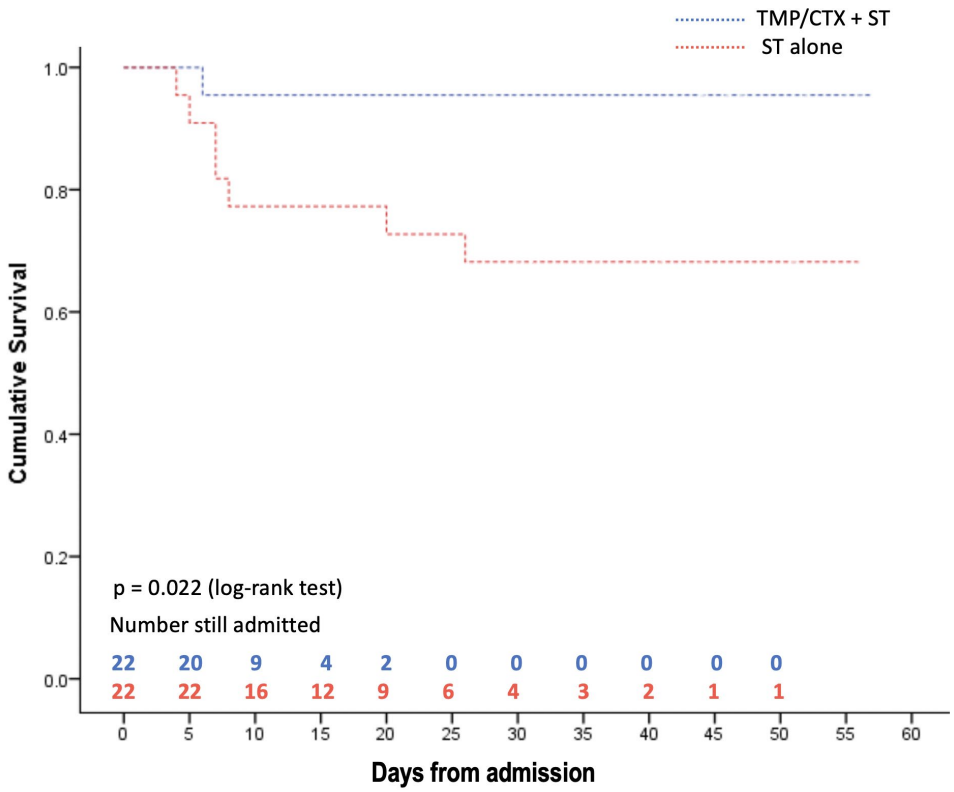
*Comparison between continuous and categorical variables was made by using Wilcoxon Signed Ranks test (for clinical parameters) / Mann-Whitney U test (for length of stay) and Chi Square test /Fishers exact test respectively. A p-value of <0.05 was considered statistically significant. $^+$SD = standard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

Figure 1: Observations between Day 0 and Day 5 in patients with severe COVID-19 receiving Trimethoprim (TMP)/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: SpO_2 = peripheral capillary *oxygen saturation; SD = standard deviation; 95% CI = 95% confidence interval; Data are presented as mean* ± SD 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)/Co-trimoxazole (CTX) with standard therapy (ST) or ST alone



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