Data from trimethoprim and cotrimoxazole in severe Covid-19 induced lung injury

Syed R. Quadery, Erin Doherty, Abishek Ray,Veronica A. Varney

•Respiratory & Immunology Dept. St Helier Hospital, Carshalton, Surrey, SM1 5AA, UK

Introduction

•In the UK, Covid-19 is now endemic with100-200 deaths per day despite 80% of the adult population being vaccinated.

•Mortality in Covid-19 is closely related to acute lung injury or ARDS (adult respiratory distress syndrome) that requires respiratory support and hospitalisation.

•There is a need for effective and inexpensive treatments that can avoid admission and speed recovery and reduce the risk of ARDS, especially for countries where health care is limited.

•We show preliminary data for the UK and India suggesting that cotrimoxazole or trimethoprim has benefit in moderate, severe and critical Covid-19 reducing mortality and hospital length of stay.

•There is also Indian data of outpatient managed Covid patients discharged with oral cotrimoxazole and oxygen showing zero mortality.

METHODS

Cotrimoxazole (CTX) and trimethoprim (TMP) block the surface FPR's(formyl peptide receptors) of neutrophil and monocytes reducing homing to the lung and neutrophil extracellular traps.
Study data in Covid-19 suggests these drugs have benefit and reduce mortality.
A TMP case series (n=44) showed mortality to be 5% with added TMP versus 32% without and LOS (length of stay) was also reduced (9 days versus 22).
India data for critical Covid-19 (n=201) showed mortality was 13% with added CTX versus 40% without; the need for ventilation was reduced by 27%. LOS was reduced (11 days versus 15).
14 patients with moderately severe Covid-19 were treated at home with oxygen and CTX, with zero mortality.
Further UK data (n=70) for TMP also suggests reduced mortality in severe Covid-19 at 28% with TMP versus 41% for standard care + recovery -2 entry.
There is an ongoing randomised study of CTX in critical Covid in India with complete data awaited.
Both CTX + TMP are inexpensive and licensed for respiratory illness and data suggests the blockade of the FPR's are the likely mechanism as to how they may reduce acute lung injury in Covid-19.

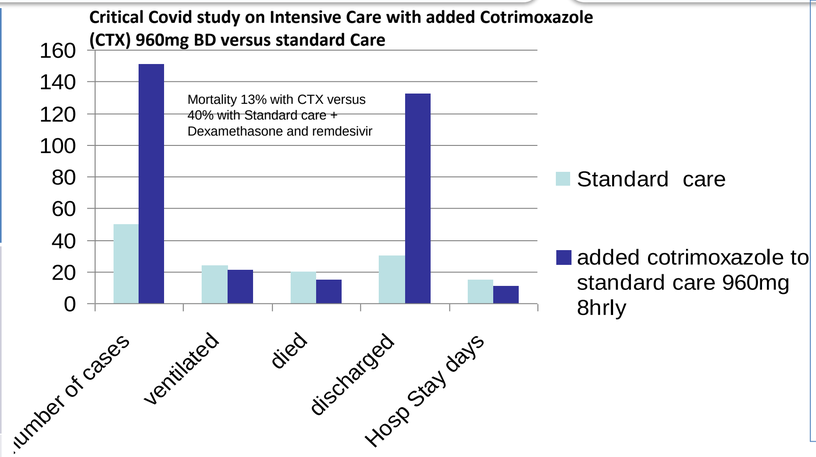
Post mortem studies show high levels of stressed neutrophils in the alveolar capillary bed extruding their nuclear material as Neutrophil Extracellular Traps or NETS (known as NETosis).
These NETS are pro-thrombotic and can block the alveolar capillary bed causing profound hypoxia and death. NETosis aims to trap infectious particles.
Neutrophils become stressed by oxygen free radicals (ROS) generated by cytokine storms due to infection, inflammation and tissue damage.
Surface formyl peptide receptors (FPR's) on neutrophils are stimulated by cytokines and free radicals giving FPR activation that can drive neutrophil NETosis.
Tissue injury and death releases formyl peptides (FP) that causes homing of neutrophils to the lung where NETosis may occur.
Monocytes also have surface FPR's and activated monocytes are reported in bronchoalveolar lavage from ventilated patients with severe Covid-19.

Results Of Studies in Covid

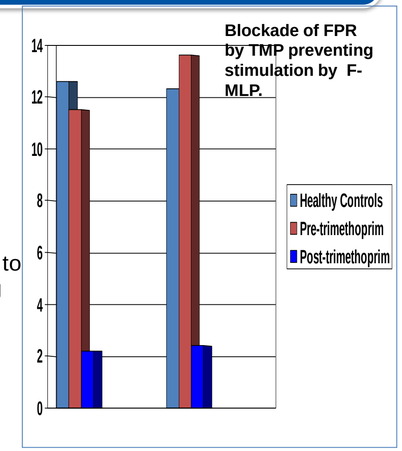
Location	Diagnosis	No of subject	Treatment cotrimoxazole (CTX) Or trimethoprim (TMP) added to standard care	Mortality % (No of Patients Pt).	% requiring invasive ventilatory support or CPAP#	Mean length of stay days ±SD Of survivors
St Helier Hospital UK (March-April 2020)	Severe Covid	22 controls* 22 CTX/TMP*	Standard antibiotics 18 Pt –TMP-5 days 4 Pt-CTX-5 days	32% (7 Pt) 4.5%(1 Pt)	73% (16Pt) 14% (3Pt)	22±13 9±4
Kolkata India (home study no beds)	Moderate Covid sent home with oxygen and CTX	14 CTX	14PT-CTX 960mg BD 10days	0%	0%	1 Pt admitted with proved enteric fever
India Medical College Hosp. W. Bengal India	Critical Covid on ITU with non-invasive ventilation	50 controls * 151 CTX*	Standard care Standard care and CTX 960mg TDS	40% (20Pt) 13% (15Pt)	42% (21Pt) 15% (24Pt)	15± 5 11± 4
St Helier Hospital UK (2021)	Severe Covid	49 control* 21 TMP*	Recovery trial + oxygen Standard antibiotics Oxygen, TMP, standard antibiotics	41% 28%	CPAP= 9 cases CPAP=7 cases	11.2 days 11.3days

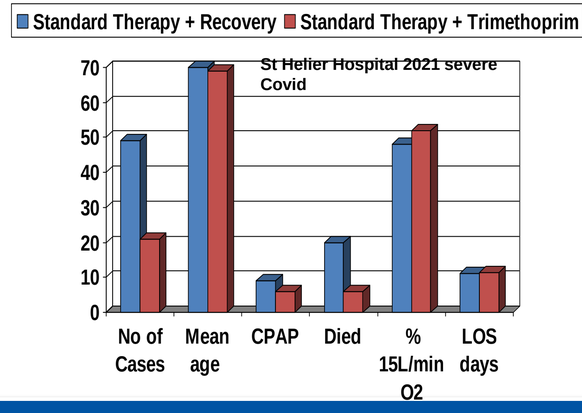
Results: using Trimethoprim (TMP) or Cotrimoxazole (CTX)

Blockade of neutrophil and monocyte surface formyl peptide receptors by trimethoprim or Cotrimoxazole following oral therapy at 7 days and flow cytometric analysis With stimulation of peptide receptors by F-Met-Leu-Phe reduced by 80-90% of expected.



Both CTX and TMP blocks the surface FPR's on circulating neutrophils (NΘ) and monocyte (MΘ) reducing homing of these cells to the lung in infection.
CTX + TMP will block activation of mononuclear cells already present in the lung.
FPR blockade will reduce intra and extra-cellular ROS and the risk of neutrophil NETosis induced lung injury.





Conclusion

•TMP or CTX reduced mortality in severe/critical Covid-19 to 5% Vs 32%.

•Home treatment for Covid-19 with CTX and oxygen showed recovery without deaths in India

•In Critical Covid patients on ITU mortality was reduced to 13% with added CTX versus 40% with standard therapy.

•A study of further severe Covid-19 patients shows a reduction in mortality of 13% with added TMP + Standard care versus ST + added treatment from the Recovery 2 study.

•Data suggests the likely Mechanism is via blockade of FPR's on neutrophils and monocytes.

The authors declare no conflict of interest

<u>Standard therapy</u>:- dexamethasone, remedesivir, Benzyl penicillin, clarithromycin, heparin prophylaxis.

Recovery :- National study randomisation

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