Dapsone as treatment adjunct in ARDS

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ABSTRACT
Multiple pharmacological interventions tested over the last decades have failed to reduce ARDS mortality. This short note recounts past data indicating that (i) neutrophils home along an IL-8 gradient, (ii) in ARDS, massive neutrophil accumulation and degranulation in and along bronchoalveolar spaces contributes to damage and hypoxia, (iii) large increases in IL-8 are one of the chemotaxic signals drawing neutrophils to the ARDS lung, and (iv) old data from dermatology and glioblastoma research showed that the old drug against Hansen's disease, dapsone, inhibits neutrophils' chemotaxis to IL-8. Therefore dapsone might lower neutrophils' contributions to ARDS lung pathology. Dapsone can create methemoglobinemia that although rarely problematic it would be particularly undesirable in ARDS. The common antacid drug cimetidine lowers risk of dapsone related methemoglobinemia and should be given concomitantly.

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Introduction
Acute respiratory distress syndrome (ARDS) continues to have a high lethality. This short note recounts past data showing that interleukin-8 (IL-8) attracts neutrophils, IL-8 increases in ARDS, and this IL-8 brings neutrophils to the lung. Those neutrophils degranulate and contribute to alveolar damage characteristic of ARDS regardless of the initial event triggering ARDS.

Dapsone has been used for over 50 years as an antibiotic. Unrelated to its attributes as antibiotic, dapsone has been used for over 20 years to treat a variety of neutrophilic dermatoses (dermatitis herpetiformis, bullous pemphigoid, et al) and rheumatoid arthritis. In the neutrophilic dermatoses dapsone works by inhibiting IL-8 mediated neutrophil chemotaxis leading ameliorating disease without effect on the underlying pathology. These observations lead to the conclusion that dapsone might ameliorate ARDS-related lung tissue destruction and improve outcomes by reducing neutrophils’ contributions without having effect on the underlying disease that triggered the ARDS.

ARDS is a severe form of acute lung injury characterized by acute diffuse bilateral pulmonary infiltration of neutrophils, monocytes and lymphocytes, diminished lung compliance, alveolar destruction, and bronchoalveolar lumen hyaline deposition, all leading to hypoxemic respiratory failure. Though there are many triggers or precipitating events leading to ARDS, f. ex. crush injury, pneumonia of any origin including Corona virus, and sepsis, the resulting pathophysiology is to some degree stereotyped. Diffuse alveolar damage is one of the characteristic, defining features of the acute phase of ARDS. Diffuse alveolar damage is characterized by edema, hyaline deposition, and dense leukocyte infiltration. Over days this is followed by an organizing phase, with septal fibrosis and pneumocyte hyperplasia. The clinical consequences of this series of events are hypoxemia and multi-organ failure with a high death rate.

Not all ARDS go on to develop diffuse alveolar damage but those who do have higher a case fatality rate. Crucially for the intended use of dapsone, Baughman et al documented by comparative study of bronchoalveolar lavage early and a second lavage late in ARDS, that a reduction in neutrophils in the second lavage predicted survival, non-reduction predicted death.
ARDS neutrophils show activation markers with excessive transendothelial migration of cytokine-primed neutrophils. IL-8 has been consistently directly correlated with the degree of neutrophil concentrations in ARDS lungs. Among other immune/inflammatory cell infiltrates, but degranulating neutrophils are pivotal to development of capillary damage with subsequent leakage, hyaline deposition and ARDS transition to the more deadly diffuse alveolar damage phase. Antibody to IL-8 inhibits development of ARDS in several different ARDS animal models. IL-8 levels with neutrophil accumulations directly correlate to ARDS severity. It is that pivotal neutrophil contribution we hope to diminish with dapsone.

Neutrophils migrate along several chemokine gradients, not just along IL-8 gradients. IL-8 is elevated in human bronchoalveolar lavage fluid of ARDS where higher lavage concentrations correlate with higher diffuse alveolar damage and mortality. Also higher lavage fluid IL-8 correlated with higher neutrophil infiltration. High circulating IL-8 characteristic of ARDS does not act alone in attracting neutrophils to the lung. IL-8 acts as part of a suite of chemokines, albeit having a central, pivotal role.

Dapsone has a long history of use in treating the neutrophilic dermatoses, rheumatoid arthritis, and use in other non-antibiotic roles. This use led to the discovery that dapsone ameliorates these dermatoses primarily by inhibiting neutrophil migration along an IL-8 gradient. Proof that the characteristic rash caused by erlotinib was mediated by IL-8 in turn led to dapsone use in treating that neutrophilic rash. In vitro study showed dapsone inhibited neutrophil chemotaxis to both N-formylmethionyl-leucyl-phenylalanine and to IL-8 via interference with neutrophils’ adherence functions.

Altogether these observations in turn led to the current suggestion of dapsone as treatment adjunct in ARDS.

Neutrophil infiltration of alveoli is present in ARDS related Coronavirus infections CoV (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV). It is probable but unproven if this is also true in COVID19 related ARDS.

Dapsone

Dapsone, a sulfone antibiotic, has been used since the 150’s to treat Mycobacterial disease and other infections including Pneumocystis, Plasmodia and others. It is on the WHO list of essential medicines. By virtue of dapsone’s ability to inhibit neutrophils’ chemotaxis to sites of inflammation, dapsone has seen wide dermatologic use in treating neutrophilic dermatoses. In an in vitro model Martin et al demonstrated activated neutrophils’ damage to pulmonary endothelium can be significantly inhibited by dapsone. They furthermore demonstrated this effect was mediated by dapsone inhibition of the neutrophil respiratory burst.

After 100 mg of oral dapsone serum concentrations between 1 and 2 mg/L are seen after 1 to 4 h. Half-life varies, from 12 to 30 h. A usual dose on the higher end would be 100 mg q 12 h.

The histamine receptor 2 blocking drug cimetidine 400 mg every 6 h or 800 mg every 12 h improves the therapeutic index by reducing dapsone N-hydroxylation. N-hydroxylation to dapsone monohydroxylamine is primarily responsible for dapsone related methemoglobinemia. Slight methemoglobinemia (<3%) is common, more severe methemoglobinemia is not common. Rarely a dapsone related hypersensitivity can be seen and that can be associated with lung injury.

Conclusion

If dapsone does work as intended here, the question remains when to start it. Too early and we risk treating people unnecessarily. Too late and damage already done. Given the severity of the current worldwide crisis with COVID19, early upon diagnosis with symptoms might be best if research indeed shows dapsone can mitigate ARDS severity. Cimetidine should be given with dapsone and methemoglobinemia must be frequently checked if dapsone is tried.
Given the high mortality of ARDS and the relatively benign nature of dapsone and cimetidine, a trial of dapsone 100 mg every 12 h plus cimetidine 400 mg every 6 h seems warranted.

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The author has no conflict of interest to declare.

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**Abbreviations**

ARDS acute respiratory distress syndrome

IL-8 interleukin-8