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ARTICLE

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.[1] 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.[1,2] 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.[3,4] The clinical consequences of this series of events are hypoxemia and multiorgan 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.[3–6] 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.[7]

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ARDS neutrophils show activation markers with excessive transendothelial migration of cytokine-primed neutrophils.[8] IL-8 has been consistently directly correlated with the degree of neutrophil concentrations in ARDS lungs.[8–10] 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.[10–12] Antibody to IL-8 inhibits development of ARDS in several different ARDS animal models.[13–16] IL-8 levels with neutrophil accumulations directly correlate to ARDS severity.[17] It is that pivotal neutrophil contribution we hope to diminish with dapsone.

Neutrophils which, when degranulated, release intracellular enzymes such as neutrophil elastase and oxidant products which participate in the alveolar-destructive process of ARDS.[18,19]

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.[20–23] Also higher lavage fluid IL-8 correlated with higher neutrophil infiltration.[22] 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.[23,24]

Dapsone has a long history of use in treating the neutrophilic dermatoses, rheumatoid arthritis, and use in other non-antibiotic roles.[25,26] This use led to the discovery that dapsone ameliorates these dermatoses primarily by inhibiting neutrophil migration along an IL-8 gradient.[27–37] Proof that the characteristic rash caused by erlotinib was mediated by IL-8 in turn led to dapsone use in treating that neutrophilic rash.[29,31,38] In vitro study showed dapsone inhibited neutrophil chemotaxis to both N-formylmethionyl-leucyl-phenylalanine and to IL-8 via interference with neutrophils' adherence functions.[37]

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).[39] 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.[25,26,40] 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.[41–43] In an in vitro model Martin et al demonstrated activated neutrophils' damage to pulmonary endothelium can be significantly inhibited by dapsone.[44] They furthermore demonstrated this effect was mediated by dapsone inhibition of the neutrophil respiratory burst.[44]

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.[40] 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.[45–49] N-hydroxylation to dapsone monohydroxylamine is primarily responsible for dapsone related methemoglobinemia.[50] Slight methemoglobinemia (<3%) is common, more severe methemoglobinemia is not common.[50] Rarely a dapsone related hypersensitivity can be seen and that can be associated with lung injury.[51]

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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Declaration of interest

The author has no conflict of interest to declare.

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References

1. Matthay MA, Zemans RL, Zimmerman GA, et al. Acute respiratory distress syndrome. *Nat Rev Dis Primers*. 2019;5(1):18. doi:10.1038/s41572-019-0069-0.
2. Liu Y, Yang Y, Zhang C, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Sci China Life Sci*. 2020;63(3):364–374. doi:10.1007/s11427-020-1643-8.
3. Cardinal-Fernández P, Lorente JA, Ballén-Barragán A, Matute-Bello G. Acute respiratory distress syndrome and diffuse alveolar damage. New insights on a complex relationship. *Annals ATS*. 2017;14(6):844–850.
4. Cardinal-Fernández P, Bajwa EK, Dominguez-Calvo A, Menéndez JM, Papazian L, Thompson BT. The presence of diffuse alveolar damage on open lung biopsy is associated with mortality in patients with acute respiratory distress syndrome: a systematic review and meta-analysis. *Chest*. 2016;149(5):1155–1164. doi:10.1016/j.chest.2016.02.635.
5. Kao KC, Chang CH, Hung CY, Chiu LC, Huang CC, Hu HC. Survival predictor in patients with acute respiratory distress syndrome and diffuse alveolar damage undergoing open lung biopsy. *PLoS One*. 2017;12(7):e0180018. e0180018.
6. Kao KC, Hu HC, Chang CH, Hung CY, Chiu LC, et al. Diffuse alveolar damage associated mortality in selected acute respiratory distress syndrome patients with open lung biopsy. *Crit Care*. 2015;19(1):228. doi:10.1186/s13054-015-0949-y.
7. Baughman RP, Gunther KL, Rashkin MC, Keeton DA, Pattishall EN. Changes in the inflammatory response of the lung during acute respiratory distress syndrome: prognostic indicators. *Am J Respir Crit Care Med*. 1996;154(1):76–81. doi:10.1164/ajrccm.154.1.8680703.
8. Chollet-Martin S, Montravers P, Gibert C, et al. High levels of interleukin-8 in the blood and alveolar spaces of patients with pneumonia and adult respiratory distress syndrome. *Infect Immun*. 1993;61(11):4553–4559.
9. Goodman RB, Strieter RM, Martin DP, et al. Inflammatory cytokines in patients with persistence of the acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 1996;154(3):602–611.
10. Matsumoto T, Yokoi K, Mukaida N, et al. Pivotal role of interleukin-8 in the acute respiratory distress syndrome and cerebral reperfusion injury. *J Leukoc Biol*. 1997;62(5):581–587. doi:10.1002/jlb.62.5.581.
11. Buttignol M, Pires-Neto RC, Rossi E Silva RC, Albino MB, Dolhnikoff M, Mauad T. Airway and parenchyma immune cells in influenza A(H1N1)pdm09 viral and non-viral diffuse alveolar damage. *Respir Res*. 2017;18(1):147. doi:10.1186/s12931-017-0630-x.
12. Sugamata R, Dobashi H, Nagao T, et al. Contribution of neutrophil-derived myeloperoxidase in the early phase of fulminant acute respiratory distress syndrome induced by influenza virus infection. *Microbiol Immunol*. 2012;56(3):171–182. doi:10.1111/j.1348-0421.2011.00424.x.
13. Mukaida N, Matsumoto T, Yokoi K, Harada A, Matsushima K. Inhibition of neutrophil-mediated acute inflammation injury by an antibody against interleukin-8 (IL-8). *Inflamm Res*. 1998;47(0):151–157.
14. Sekido N, Mukaida N, Harada A, Nakanishi I, Watanabe Y, Matsushima K. Prevention of lung reperfusion injury in rabbits by a monoclonal antibody against interleukin-8. *Nature*. 1993;365(6447):654–657.
15. Yokoi K, Mukaida N, Harada A, Watanabe Y, Matsushima K. Prevention of endotoxemia-induced acute respiratory distress syndrome-like lung injury in rabbits by a monoclonal antibody to IL-8. *Lab. Invest*. 1997;76(3):375–384.
16. Bao Z, Ye Q, Gong W, Xiang Y, Wan H. Humanized monoclonal antibody against the chemokine CXCL-8 (IL-8) effectively prevents acute lung injury. *Int Immunopharmacol*. 2010;10(2):259–263.
17. Aggarwal A, Baker CS, Evans TW, Haslam PL. G-CSF and IL-8 but not GM-CSF correlate with severity of pulmonary neutrophilia in acute respiratory distress syndrome. *Eur Respir J*. 2000;15(5):895–901. doi:10.1034/j.1399-3003.2000.15e14.x.
18. Groeneveld AB, Raijmakers PG, Hack CE, Thijs LG. Interleukin 8-related neutrophil elastase and the severity of the adult respiratory distress syndrome. *Cytokine*. 1995;7(7):746–752. doi:10.1006/cyto.1995.0089.
19. Strieter RM, Kunkel SL. Acute lung injury: the role of cytokines in the elicitation of neutrophils. *J. Investig. Med*. 1994;42(4):640–651.

20. Miller EJ, Cohen AB, Nagao S, et al. Elevated levels of NAP-1/interleukin-8 are present in the airspaces of patients with the adult respiratory distress syndrome and are associated with increased mortality. *Am Rev Respir Dis*. 1992;146(2):427–432. doi:10.1164/ajrccm/146.2.427.
21. Stapleton RD, Suratt BT, Neff MJ, et al. Bronchoalveolar fluid and plasma inflammatory biomarkers in contemporary ARDS patients. *Biomarkers*. 2019;24(4):352–359. doi:10.1080/1354750X.2019.1581840.
22. Nys M, Deby-Dupont G, Habraken Y, et al. Bronchoalveolar lavage fluids of ventilated patients with acute lung injury activate NF-kappaB in alveolar epithelial cell line: role of reactive oxygen/nitrogen species and cytokines. *Nitric Oxide*. 2003;9(1):33–43. doi:10.1016/j.niox.2003.07.001.
23. Williams AE, José RJ, Mercer PF, et al. Evidence for chemokine synergy during neutrophil migration in ARDS. *Thorax*. 2017;72(1):66–73.
24. Ikuta N, Taniguchi H, Kondoh Y, Takagi K, Hayakawa T. Sustained high levels of circulatory interleukin-8 are associated with a poor outcome in patients with adult respiratory distress syndrome. *Intern Med*. 1996;35(11):855–860.
25. Wozel VE. Innovative use of dapsone. *Dermatol Clin*. 2010;28(3):599–610. doi:10.1016/j.det.2010.03.014.
26. Wozel G, Blasum C. Dapsone in dermatology and beyond. *Arch Dermatol Res*. 2014;306(2):103–124. doi:10.1007/s00403-013-1409-7.
27. Karpel-Massler G, Kast RE, Siegelin MD, et al. Anti-glioma activity of dapsone and its enhancement by synthetic chemical modification. *Neurochem Res*. 2017;42(12):3382–3389. doi:10.1007/s11064-017-2378-6.
28. Bellon H, Vandermeulen E, Mathyssen C, et al. Interleukin-1α induced release of interleukin-8 by human bronchial epithelial cells in vitro: assessing mechanisms and possible treatment options. *Transpl Int*. 2017;30(4):388–397.
29. Boccellino M, Quagliuolo L, Alaia C, et al. The strange connection between epidermal growth factor receptor tyrosine kinase inhibitors and dapsone: from rash mitigation to the increase in anti-tumor activity. *Curr Med Res Opin*. 2016;32(11):1839–1848.
30. Marzano AV, Tavecchio S, Berti E, Gelmetti C, Cugno M. Cytokine and chemokine profile in amicrobial pustulosis of the folds: evidence for autoinflammation. *Medicine (Baltimore)*. 2015;94(50):e2301. doi:10.1097/MD.0000000000002301.
31. Kast RE. Erlotinib augmentation with dapsone for rash mitigation and increased anti-cancer effectiveness. *Springerplus*. 2015;4(1):638. doi:10.1186/s40064-015-1441-5.
32. Lan CC, Wu CS, Huang SM, Wu IH, Chen GS. High-glucose environment enhanced oxidative stress and increased interleukin-8 secretion from keratinocytes: new insights into impaired diabetic wound healing. *Diabetes*. 2013;62(7):2530–2538. doi:10.2337/db12-1714.E.
33. Kast RE, Lefranc F, Karpel-Massler G, Halatsch ME. Why dapsone stops seizures and may stop neutrophils' delivery of VEGF to glioblastoma. *Br J Neurosurg*. 2012;26(6):813–817. doi:10.3109/02688697.2012.674577.
34. Kast RE, Scheuerle A, Wirtz CR, Karpel-Massler G, Halatsch ME. The rationale of targeting neutrophils with dapsone during glioblastoma treatment. *Anticancer Agents Med Chem*. 2011;11(8):756–761. doi:10.2174/187152011797378805.
35. Kanoh S, Tanabe T, Rubin BK. Dapsone inhibits IL-8 secretion from human bronchial epithelial cells stimulated with lipopolysaccharide and resolves airway inflammation in the ferret. *Chest*. 2011;140(4):980–990.
36. Schmidt E, Reimer S, Kruse N, Bröcker EB, Zillikens D. The IL-8 release from cultured human keratinocytes, mediated by antibodies to bullous pemphigoid autoantigen 180, is inhibited by dapsone. *Clin Exp Immunol*. 2001;124(1):157–162.
37. Booth SA, Moody CE, Dahl MV, Herron MJ, Nelson RD. Dapsone suppresses integrin-mediated neutrophil adherence function. *J Invest Dermatol*. 1992;98(2):135–140.
38. Bangsgaard N, Houtkamp M, Schuurhuis DH, et al. Neutralization of IL-8 prevents the induction of dermatologic adverse events associated with the inhibition of epidermal growth factor receptor. *PLoS One*. 2012;7(6):e39706. doi:10.1371/journal.pone.0039706.
39. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol*. 2017;39(5):529–539. doi:10.1007/s00281-017-0629-x.
40. Molinelli E, Paolinelli M, Campanati A, Brisigotti V, Offidani A. Metabolic, pharmacokinetic, and toxicological issues surrounding dapsone. *Expert Opin Drug Metab Toxicol*. 2019;15(5):367–379.
41. Gusdorf L, Lipsker D. Neutrophilic urticarial dermatosis: an entity bridging monogenic and polygenic autoinflammatory disorders, and beyond. *J Eur Acad Dermatol Venereol*. 2020;34(4):685–690. doi:10.1111/jdv.15984.
42. Roman C, Dima B, Muyshont L, Schurmans T, Gilliaux O. Indications and efficiency of dapsone in IgA vasculitis (Henoch-Schonlein purpura): case series and a review of the literature. *Eur J Pediatr*. 2019;178(8):1275–1281.
43. Ghaoui N, Hanna E, Abbas O, Kibbi AG, Kurban M. Update on the use of dapsone in dermatology. *Int J Dermatol*. 2020. [Epub ahead of print] doi:10.1111/ijd.14761.
44. Martin WJ, 2nd, Kachel DL. Reduction of neutrophil-mediated injury to pulmonary endothelial cells by dapsone. *Am Rev Respir Dis*. 1985;131(4):544–547. doi:10.1164/arrd.1985.131.4.544.

45. Coleman MD. Dapsone: modes of action, toxicity and possible strategies for increasing patient tolerance. *Br J Dermatol*. 1993;129(5):507–513. doi:10.1111/j.1365-2133.1993.tb00476.x.
46. Coleman MD, Scott AK, Breckenridge AM, Park BK. The use of cimetidine as a selective inhibitor of dapsone N-hydroxylation in man. *Br J Clin Pharmacol*. 1990; 30(5):761–767. doi:10.1111/j.1365-2125.1990.tb03847.x.
47. Coleman MD, Rhodes LE, Scott AK, et al. The use of cimetidine to reduce dapsone-dependent methaemoglobinaemia in dermatitis herpetiformis patients. *Br J Clin Pharmacol*. 1992;34(3):244–249.,. doi:10.1111/j.1365-2125.1992.tb04131.x.
48. Goolamali SI, Macfarlane CS. The use of cimetidine to reduce dapsone-dependent haematological side-effects in a patient with mucous membrane pemphigoid. *Clin Exp Dermatol*. 2009;34(8):e1025–6. doi:10.1111/j.1365-2230.2009.03710.x.
49. Rhodes LE, Tingle MD, Park BK, et al. Cimetidine improves the therapeutic / toxic ratio of dapsone in patients on chronic dapsone therapy. *Br J Dermatol*. 2006;132(2):257–262. doi:10.1111/j.1365-2133.1995.tb05022.x.
50. Barclay JA, Ziemba SE, Ibrahim RB. Dapsone-induced methemoglobinemia: a primer for clinicians. *Ann Pharmacother*. 2011;45(9):1103–1115. doi:10.1345/aph.1Q139.
51. Kinehara Y, Kijima T, Inoue K, et al. Dapsone hypersensitivity syndrome-related lung injury without eosinophilia in the bronchoalveolar lavage fluid. *Intern Med*. 2015;54(7):827–831. doi:10.2169/internalmedicine.54.3406.

Abbreviations

ARDS	acute respiratory distress syndrome
IL-8	interleukin-8