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Myeloperoxidase inhibition: potential therapeutic target for crescentic glomerulonephritis?

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Background: Myeloperoxidase (MPO) released following neutrophil and monocyte activation can lead to host tissue damage by generating reactive oxygen species and promoting further leukocyte activation. Extracellular glomerular MPO deposition has been shown in ANCA- associated vasculitis (AAV) and may aggravate disease by promoting adaptive immunity through antigen specific T and B cell activation, enhancing crescentic glomerulonephritis (CGN). While, MPO deficient animals have attenuated glomerulonephritis, they have augmented T cell responses. We investigated the impact of pharmacological inhibition of MPO in vitro and in vivo using a novel MPO inhibitor, AZM198, to understand its potential role in the treatment of CGN.

Methods: A) We stained renal biopsies for MPO and CD15 from patients with CGN due to Systemic Lupus Erythematosous, IgA, anti-glomerular basement membrane disease, ANCA negative and ANCA positive GN. B) We measured MPO concentration in the plasma of AAV patients and healthy controls and MPO activity and neutrophil degranulation following stimulation by cytokines or ANCA in the absence and presence of AZM198. C) We assessed the effect of MPO inhibition on endothelial damage induced by ANCA -primed neutrophils. D) We induced nephrotoxic nephritis in mice and investigated the effect of AZM198 on CGN severity and antigen-specific T cell reactivity.

Results: All biopsies with CGN had extracellular glomerular MPO deposition. MPO deposition significantly correlated with clinical features (eGFR (r= -0.85), proteinuria (r=0.74)), percentage of crescents (r =0.64), and interstitial fibrosis and tubular atrophy (r=0.79)). In vitro, addition of AZM198 led to a significant reduction in MPO activity, released human neutrophil peptide levels, measured in the supernatants of cytokine and ANCA- stimulated neutrophils, and attenuated neutrophil-mediated EC damage. In vivo, delayed AZM198 treatment reduced proteinuria, glomerular thrombosis, serum creatinine (all, $p<0.05$), and glomerular macrophage infiltration ($p<0.01$), without promoting an increase in adaptive T cell responses. (Figure1)

Conclusion: MPO inhibition reduced AAV patient neutrophil degranulation and attenuated neutrophil-mediated EC damage. In a preclinical model of CGN, delayed MPO inhibition suppressed kidney damage without augmenting adaptive immune responses, suggesting it may be a novel adjunctive therapy in various forms of CGN.

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