Conclusion: Machine learning models based on transcriptomic functional pathways can accurately predict response to tofacitinib. Our study could contribute to improve the treatment customization and the optimization of RA treatment strategy toward a personalized approach. Furthermore, these findings may help to understand the mechanisms underlying the clinical response to JAK inhibitors.

Disclosure of Interests: None declared.

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The Yin and Yang of scleroderma and vasculitis

Preclinical studies of a novel cathepsin C inhibitor in MPO-ANCA-associated vasculitis model

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Background: MPO-ANCA-associated vasculitis (MPO-AAV) is a systemic small vessel vasculitis with the production of MPO-ANCA in the serum. This disease develops necrotizing and crescent glomerulonephritis (NCGN) and peritubular capillaritis-mediated interstitial damages in the kidneys, and pulmonary hemorrhage due to capillaritis in the lungs. Recent studies have revealed that neutrophil extracellular traps (NETs) induced by MPO-ANCA are critically involved in its pathogenesis, and neutrophil elastase (NE) plays an essential role in the activation process of several neutrophil serine proteases (NSPs) such as NE, proteinase 3 and cathepsin G by converting the inactive forms of the NSPs to the active forms by digesting dipeptides at the N-terminus of the enzymes.2

Objectives: Although glucocorticoids and immunosuppressive drugs used as the standard of cares can lead remission in MPO-AAV patients, there are remaining unmet medical needs such as severe side effects, resistance to the treatment and relapse. Therefore, development of new therapeutic strategies is awaited. The aim of this study is to demonstrate the efficacy of MOD06051, a novel CatC inhibitor, against MPO-AAV, using an MPO-AAV rat model established previously.3

Methods: In vitro studies: Cathpsins and NE inhibitory activity was measured using recombinant enzymes and fluorescent substrates. Cellular NE activity in human MPO according to Little's protocol.4 The rats were divided into three groups (n=8 in each group), and vehicle (0.5% methylcellulose) or MOD06051 (0.3 or 3 mg/kg bid) was orally administered every day for 42 days. All rats were euthanized at the end of the study for serological and histological evaluations.

Results: In vitro studies: MOD06051 inhibited the enzymatic activity of human recombinant CatC with an IC50 value of 1.5 nM, and no other cathespins nor NE inhibition was observed at 10 μM. The NE activity in primary human granulocytes was suppressed by MOD06051 treatment in a dose-dependent manner. Furthermore, hematuria score, urinary NGAL (Neutrophil Gelatinase-Associated Lipocalin), tubular erythrocyte cast counts, and pulmonary hemorrhage foci were significantly decreased in the 3 mg/kg of MOD06051 treated group with the similar trends in 0.3 mg/kg group.

Conclusion: MOD06051 showed specific inhibition of CatC activity. This compound suppressed the serine proteases activation in primary human neutrophils and NET formation in the MPO-AAV model rats, resulting in amelioration of MPO-ANCA-induced tissue destruction, including NCGN and tubular interstitial damages in the kidneys, and disorder of alveolar septal capillaries in the lungs. MOD06051 appears to be a promising agent for treatment of MPO-AAV patients.


References: