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The Hunt for New Targets for Treatment of Active ANCA Vasculitis

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In the recent article by Dooley et al. [1], the effects of EDO-S101 (an alkylating fusion histone deacetylase inhibitor molecule) were studied in a passive mouse model of anti-myeloperoxidase IgG-induced glomerulonephritis and an active rat model of myeloperoxidase-ANCA (Anti-Neutrophil Cytoplasmic Antibodies) microscopic polyangiitis. Pretreatment with EDO-S101 reduced circulating leucocytes did not prevent the development of passive IgG-induced glomerulonephritis in mice; however treatment in rats with active experimental ANCA vasculitis significantly reduced glomerulonephritis and lung hemorrhage. EDO-S101 significantly depleted rat B and T cells, as well as inducing DNA damage and apoptosis in proliferating human B cells, suggesting a selective effect on the adaptive immune response.

The need for new treatments for ANCA-associated vasculitis has become urgent in the face of increasing evidence of significant morbidity associated with the existing staples of vasculitis management, including prolonged courses of high dose corticosteroids and cyclophosphamide [2]. Histone deacetylase inhibitors (HDACis) represent a new class of immunosuppressive medications, first described in oncology literature in 2006 [3]. They act by targeting histone deacetylase enzymes that remove the acetyl groups from lysine residues, leading to chromatin condensation and transcription silencing. They repress B- and T-cell transcription factors through histone hyperacetylation, which selectively affects reduces gene transcription for these cells, while enhancing the activity of other transcription factors such as p53. Recently, HDACis have been shown to ameliorate the effects of inflammation in rodent models of arthritis, asthma and colitis; however their mechanisms of action have not been well-described [4].

EDO-S101 was developed by Mundipharma EDO GmbH and is an alkylating HDACi fusion molecule that combines the effects of bendamustine with a fully functional potent and reversible pan-HDACi, vorinostat [5]. The combination of 2 drugs allows for greater efficiency at a lower dose of the alkylating agent due to a bifunctional mode of action. HDAC inhibition increases the ability of the alkylating moiety to access DNA double strands by opening chromatin. This therefore creates a synergy between the two compounds. EDO-S101 has been found to be well tolerated and acts efficiently against hematological malignant neoplasia and solid tumors [5-8].

Here, Dooley et al. [1] have assessed the efficacy of EDO-S101 in 2 well-established rodent models of AAV (adeno-associated virus) which differ significantly in their modes of disease induction: a passive mouse model of anti-MPO (Anti-myeloperoxidase) IgG induced GN (Glomerulonephritis), invoking innate immunity in its response to the disease antigen, and a an active rat model of experimental autoimmune vasculitis (EAV). EAV is an MPO-ANCA vasculitis model induced by immunization of Wistar Kyoto rats with anti-human MPO (hMPO), which thereby provokes changes in adaptive immunity resulting in phenotypic manifestations of active ANCA vasculitis. These features of mild pauci-immune vasculitis, including glomerulonephritis and lung hemorrhage, are indistinguishable pathologically from human vasculitis, making EAV a valuable preclinical model in AAV.

The authors first demonstrate the mechanism by which EDO-S101 induces DNA damage through global histone 3 hyperacetylation in HL60 cells using specific antibodies for acetylated lysine residues in total cell extracts of HL60 cells. A strong simultaneous DNA repair response was demonstrated in tumour samples taken from mice with subcutaneous human Daudi Burkitt lymphoma, through activation of ataxia telangiectasia mutated (ATM) kinase and Rad3-related protein (ATR), leading to downstream activation of checkpoint kinase 1 and 2. Interestingly, EDO-S101 had no effect on anti-MPO induced vasculitis in the passive transfer mouse model of MPO-AAV. Circulating anti-MPO antibodies levels were unchanged for mice that were pre-treated with EDO-S101 and there was no difference in the development of hematuria and glomerulonephritis between vehicle and EDO-S101 treated mice, though there was a slight reduction in albuminuria for those that had been pre-treated with EDO-S101. The effect of EDO-S101 in the active rat model of EAV was far more significant, with a significant reduction of anti-MPO titer between vehicle and treated rats at D56 post immunization with MPO, as well as significant reductions in albuminuria and hematuria seen. There was a dramatic improvement in glomerulonephritis and lung hemorrhage seen in association with this.

The authors went on to look at cellular correlates using flow cytometry. They found an increase in both monocyte and neutrophil fractions by D7 in EDO-S101 treated mice, indicating a sparing of this cell type relative to other leucocytes. The relative sparing of neutrophils by EDO-S101 can therefore potentially explain the lack of effect on disease phenotype in the passive transfer mouse model; leading this compound to be ineffective in a neutrophil-dependent murine model. A similar relative increase in the neutrophil fraction was also noted in EDO-S101 treated rats with EAV. There was no significant effect on NK cell fraction after treatment with EDO-S101. However, EDO-S101 was found to reduce B-cell viability and proliferation and to increase B cell subdiploid cell populations, cleaved poly (ADP-ribose) polymerase (PARP) levels and propidium iodide staining, in keeping with a clear effect on the adaptive immune system. There was also evidence induction of both p53 and pH2AX DNA damage markers in spleen tissue from rats treated with EDO-S101, indicating increased apoptosis in EDO-S101 treated B cells and in EAV spleen tissue.

These results are exciting in providing greater evidence for the role of HDACis in potentiating the work of low dose alkylating agents, such as bendamustine, to induce remission for AAV while reducing the risk of associated side-effects and risk for relapse once treatment is discontinued. Dooley et al. [1] have efficiently shown that the main beneficial effects of EDO-S101 on the immune system are mediated by suppression of B and T cell proliferation as part of the adaptive immune response following active immunization with MPO in rats. They have also demonstrated induction of DNA damage by EDO-S101 as a result of hyperacetylation of lysine residues of the histone 3 tail in extracts of HL60 cells and that this acetylation capacity exceeded that of bendamustine alone. In EAV spleen tissue, induction of DNA damage markers, p53 and pH2AX were noted simultaneously with suppression of homologous DNA repair (p-ATR and p-ATM suppression). Increased PARP cleavage and the presence of increased subdiploid DNA in human B cells also indicated increased apoptosis induced by EDO-S101, significantly more potent than at equimolar concentrations of bendamustine and vorinostat.

Given the body of evidence that already exists for the potent therapeutic effect of EDO-S101 on human hematological malignancies, solid organ tumours and on the adaptive immune system in inflammatory disease, this work by Dooley et al. [1] adds further plausibility to the potential role for HDACis in inducing remission in AAV through suppression of B and T cell effects. It provides encouraging evidence for HDAC is as a novel class of immunosuppressive agent that can be used in conjunction with existing therapies for AAV in order to lower the cumulative dose given of each individual agent to reduce the risk associated with exposure to these regimens. Further information about the side-effect profile of HDAC is and their long-term toxicity and tolerability will be pivotal in helping to determine the utility of this therapy for our vasculitis patients.

This work is limited in that both rodent models provide only a mild AAV disease phenotype and cannot therefore fully approximate human disease. Nevertheless, the work that has been done here is invaluable in further illustrating mechanistic effects of EDO-S101 on key aspects of AAV pathogenesis, particularly its effects on the adaptive immune system. Further animal and human studies are eagerly anticipated to determine an optimal dosing strategy, whether an orally active form of the medication can be developed, and whether the bifunctional model could reduce the risk of infectious complications through reducing total exposure to either immunosuppressive component. Finally, a trial of EDO-S101 in combination with, or against, an existing immunosuppressive regimen for induction of remission in AAV will be crucial to determine the relative efficacy of this medication in the overall management of this life-threatening condition and the many complications that attend its treatment strategies.

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