COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

An Anti-inflammatory Treatment Strategy To Ameliorate The Pathogenic Effects Of Venezuelan Equine Encephalitis Virus Infection.

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As evidenced by the fact that the first drug worldwide to be licenced to treat COVID-19 was an anti-inflammatory, there is increased interest in strategies that prevent infection-induced immuno-pathology. In a layered defence strategy, anti-inflammatories could be used alongside therapies that target biological warfare agents directly to prevent spread and replication.
Here we used the well-established Balb/c subcutaneous mouse model of VEEV infection. Here mice exhibit clear clinical signs of infection, including invariant neurological deficits (encephalitis) and weight loss, and succumb to infection within 7 days.
Firstly, robust inflammatory correlates of brain pathology were identified using two independent time-course experiments. Concentrations of the inflammatory proteins CCL-2, CCL-5 and TNF-α and the abundance of CD45+ cells in the brain all correlated with brain pathology to a very high degree (Pearson's R>0.9). These markers were then used to screen regimens of representatives from all major groups of clinically in-use anti-inflammatory drugs (biologics, non-steroidal anti-inflammatory drugs (NSIADS), COX-2 inhibitors, corticosteroids and janus kinase inhibitors). The strong inflammation driven by VEEV infection was very resistant to therapeutic intervention with the anti-inflammatory drugs and initial regimens selected, and there was no statistical evidence to demonstrate their ability to alter any of the identified markers. The initial dose of the corticosteroid Dexamethasone was 1mg/kg, a mouse equivalent dose to that reported to have been used to treat severe COVID-19. A fifty-fold increase of Dexamethasone was necessary to demonstrate an anti-inflammatory effect in this lethal VEEV model ($p<0.001$). This effect included reduction in TNFα of over four fold. Observations also included a reduction in weight loss & clinical signs early in disease followed by a measureable but small increase in viral titres and clinical signs very late in the disease process. This suggests that whilst the inflammatory response is dampened, possibly resulting in a transiently improved clinical outcome (first few days of disease) the infection remains rampant. Next steps should seek to explore the layered defence potential of combination therapy with an antiviral (e.g. small molecule or mAb); a strategy with proven efficacy against COVID-19 infection. Such a strategy may have the potential to be pathogen-agnostic as a first layer of treatment for biological warfare agents.