Pirfenidone, an alternative treatment to glucocorticosteroids for viral-induced exacerbations?

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Introduction. Patients with respiratory diseases experience increased susceptibility to and severity of viral infections, potentially driven by the combined immunosuppressive actions of elevated lung transforming growth factor-beta (TGFβ), prophylactic inhaled glucocorticosteroids (GCS) and oral GCS used during exacerbations. Emerging evidence suggests the anti-fibrotic and anti-inflammatory drug pirfenidone (PFD) may provide a novel, non-immunosuppressive alternative (Thomas, 2025). Moreover, administration by inhalation may limit side effects while maintaining efficacy.
Aims. To compare the efficacy of inhaled PFD to GCS in the context of viral-induced lung exacerbations.
Methods. Transgenic TGFβ overexpressing mice (Chitty, 2025) were treated intranasally daily with vehicle (control), PFD (13.3 mg/kg) or GCS (fluticasone propionate, 1 mg/kg) from 2 days prior to infection with Influenza A virus (IAV, 10^2 PFU, HKx31) and up to 3 days post-infection (n=5-12). Viral loads in lung homogenates were quantified by plaque assay, BALF inflammatory cells and cytokines assessed by cell counts and ELISA, and innate immune genes by RT-PCR.
Results. Daily administration of PFD, but not GCS, reduced TGFβ-enhanced viral load by over 50% ($p<0.001$). In BALF, viral-induced increase in chemokine RANTES was reduced by both PFD and GCS, however, only PFD reduced cytokines IL-6 and TNFα ($p<0.01$). Only GCS worsened viral-induced inflammatory cell infiltration, predominantly macrophages and neutrophils ($p<0.01$). Lastly, GCS, but not PFD, suppressed innate immune genes *Ifnλ2, Isg-15* and *Ifit-1* ($p<0.01$).
Discussion. PFD afforded superior protection against TGFβ-enhanced viral infection severity and inflammation compared to the current standard of care, GCS. Comparisons of PFD and GCS using prophylactic inhaled regimens and post-infection oral treatments are underway to better mimic clinical practice. Positive findings will support the repurposing of PFD to reduce infection susceptibility, severity, and the associated lung damage in patients during exacerbations of pre-existing respiratory diseases.

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