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Summary

JAK1 BLOCKADE AMELIORATES DISEASE SEVERITY IN IMMUNE CHECKPOINT INHIBITOR-INDUCED COLITIS

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IFNγ/JAK1 signalling is upregulated in immune checkpoint inhibitor-induced colitis, and JAK1 inhibition with Upadacitinib ameliorated disease in preclinical models and achieved complete mucosal healing in eight treatment-refractory patients.

KEY POINTS

- Gene expression profiling of colonic biopsies from CPI-colitis patients identified IFNγ signalling as the top enriched pathway, with IFNγ-responsive transcripts including CXCL9, CXCL10, IDO1, GZMB and STAT1 among the most upregulated.
- In two murine models of CPI-colitis, Upadacitinib administration significantly reduced colon mass, infiltrating neutrophils, inflammatory monocytes, and CD8+ T cells producing cytotoxic cytokines.
- Colonic organoids from CPI-colitis patients expressed high baseline IFNγ-responsive transcripts and showed destruction when treated with IFNγ alone, but survived and showed continued differentiation when co-treated with Upadacitinib.
- All eight patients with severe, treatment-refractory CPI-colitis treated with Upadacitinib 45mg for eight weeks achieved rapid resolution of disease, complete mucosal healing, and significant decreases in CTCAE grade and faecal calprotectin.
- This work is relevant to clinicians managing patients with severe or refractory immune checkpoint inhibitor-induced colitis.

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