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Efzofitimod: a novel therapeutic candidate for SSc-ILD

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Systemic sclerosis-associated interstitial lung disease (SSc-ILD) is an autoimmune disease characterized by inflammation and fibrosis of skin and lungs. Efzofitimod is an immunomodulator that has demonstrated clinical proof-of-concept (POC) in pulmonary sarcoidosis, a related ILD. In animal models of ILD, including SSc-ILD, efzofitimod reduced inflammation and fibrosis. Efzofitimod binds to neuropilin-2 (NRP2), a membrane protein upregulated at sites of inflammation, most notably on myeloid cells which are involved in the pathology of both sarcoidosis and SSc-ILD. NRP2 has previously been shown to be highly expressed in myeloid cells within sarcoidosis granulomas. We aimed to explore the therapeutic potential of efzofitimod in SSc-ILD by evaluating myeloid cells from SSc-ILD patients. NRP2 was highly expressed on macrophages in skin from scleroderma patients. Similar to sarcoidosis, circulating monocytes from SSc-ILD patients expressed higher levels of NRP2 than healthy donors, exhibited a dysregulated CCR2/CCL2 signaling axis, secreted high levels of pro-inflammatory cytokines at baseline and responded abnormally to LPS compared to healthy donors. Efzofitimod downregulated inflammatory cytokines and receptors on primary monocyte-derived macrophages, including CD14, a membrane protein for which high expression is associated with progression of SSc disease. Given the similarities observed between myeloid responses of SSc-ILD and sarcoidosis and the anti-inflammatory effect of efzofitimod on myeloid cells, together with its anti-inflammatory and anti-fibrotic effects in animals and clinical POC in sarcoidosis, efzofitimod is a promising therapeutic candidate for SSc-ILD with a novel mechanism of action.

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