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IL-1 receptor antagonist restores IL-18 NK cell axis in systemic JIA

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Background

Systemic onset juvenile idiopathic arthritis (SoJIA) is an acquired auto-inflammatory disease characterized by systemic inflammation and innate immune activation reflected by uncontrolled production of cytokines such as IL-1, IL- 6 and IL-18. In SoJIA, NK cell function is severely hampered despite high levels of IL-18.

We recently found that defective phosphorylation of the IL-18 receptor beta is responsible for the deficient IL-18-NK cell axis in SoJIA.

Aim

To study first line treatment with recombinant IL-1 receptor antagonist (rIL-1RA, Anakinra) in 16 newly diagnosed and steroid naïve systemic onset JIA patients.

Materials and methods

Clinical outcome was measured using ACRp70 and ACRp90. Furthermore, NK cell lytic function, inflammasome activity and cytokine levels in plasma were assessed during follow up (max 3 years).

Results

Here we show that patients with SoJIA have increased inflammasome activation leading to elevated IL-18 levels. First line treatment in steroid naïve patients, with rIL-1RA effectively down-regulated IL-18 levels through suppression of inflammasome activation and led to rapid resolution of clinical features in 87% (ACRp90) of patients. Furthermore, using rIL-1RA as first line treatment approach the defective IL-18-NK cell axis is restored as shown by improved lytic NK cell function and regaining of the NK cell responsiveness to IL-18 stimulation.

Conclusions

These data suggest that the mechanisms of inflammatory control induced by rIL-1RA in SoJIA patients involves more than blocking IL-1R. Our data show that rIL-1RA directly targets the inflammasome and restores the IL-18 NK cell axis as well.

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