ADIPONECTIN STIMULATES PRO-INFLAMMATORY CYTOKINE PRODUCTION BY PERIPHERAL BLOOD MONONUCLEAR CELLS FROM PATIENTS WITH EARLY UNTREATED RHEUMATOID ARTHRITIS

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Background: The pathogenesis of rheumatoid arthritis (RA) involves the action of immune cells and fibroblast-like synoviocytes (FLS). Adiponectin, an adipokine produced mainly by adipocytes, is elevated in serum of RA patients compared to healthy controls; moreover, synovial fluid from RA subjects has higher levels of adiponectin compared to controls with osteoarthritis1,2. Adiponectin induces the production of pro-inflammatory cytokines, such as interleukin 6 (IL-6) and IL-8, by

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REMOVED STEROIDOGENIC ACTIVITY OF REPOSITORY CORTICOTROPIN INJECTION (RCI) INDUCES A DISTINCT CYTOKINE RESPONSE FOLLOWING T CELL ACTIVATION IN VIVO

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Background: Melanocortin receptor agonists, such as oleanolic acid, have been shown to reduce inflammation in preclinical models, suppressing the production of pro-inflammatory cytokines. Natural and synthetic ACTH analogues remain linked to the induction of corticosteroids as their primary mechanism of action, leading to the anti-inflammatory and immunosuppressive responses. Repository Corticotropin Injection (RCI) is a complex mixture containing purified porcine pituitary ACTH-analogue, and is an FDA-approved treatment for several inflammatory diseases. RCI has been shown to be effective in steroid-refractory autoimmune diseases.

Objectives: We hypothesize that Acthar has an immune regulatory response distinct from synthetic ACTH and steroids. These studies sought to explore the differences between RCI and synthetic ACTH on corticosterone levels in rats and cytokine production in a murine T cell activation model.

Methods: RCI (10, 40, or 400 IU/kg) or ACTH (0.6, 1.2, or 2.4 mg/kg) was administered to Sprague Dawley rats, plasma samples collected and analyzed for corticosterone. To determine the effect on T cell cytokine production, Balb/C mice were treated with RCI (10, 40, and 400 IU/kg), ACTH (0.6, 1.2, or 2.4 mg/kg) or prednisolone 1 hour prior to the administration of an anti-CD3. Two hours after antibody administration, plasma cytokines were measured using Meso Scale multiplex ELISA.

Results: RCI and ACTH peak corticosterone and area under the curve (AUC) were evaluated. RCI-induced corticosterone rapidly peaked between 2-8 hrs. and was dependent on the dose. ACTH displays a delay in the peak time (8-24 hours) and was not dose dependent. When compared to the high dose ACTH, RCI reduced the AUC by 50.0 ± 2.6%, 45.5 ± 5.6% and 27.3 ± 12.5% respectively for 10, 40, and 400 IU/kg. However, there was no significant reduction between any of the ACTH doses tested.

To further explore functional differences between RCI and ACTH, we examined the effects on T cell activation. In vivo T cell activation with the anti-CD3 antibody (clone, 145-2C11) increased several cytokines, including IL-2, IL-6, IL-10, and IFNγ. Treatment with RCI, ACTH, or prednisolone significantly reduced the production of IL-2, IL-4, IFNγ, and TNFα. Interestingly, RCI showed an inverse dose-response on the production of IL-6 and IL-10. RCI inhibited the production of IL-6 at 74.7 ± 4.4% and 67.9 ± 8.5% and IL-10 at 39.1 ± 7.1% and 26.7 ± 9.3% for 10 and 40 IU/kg, respectively, whereas 400 IU/kg had no effect. ACTH inhibited the production of IL-6 at a similar level for all doses tested and had no effect on IL-10 production, whereas treatment with prednisolone inhibited all cytokines.

Conclusion: These data show that RCI has a reduced steroidal response compared to synthetic ACTH. RCI has a direct and distinct immunomodulatory response on T cells unique from both synthetic ACTH and steroids. These characteristic effects suggest a mechanism of action for RCI that is steroid-independent and may help explain its benefit in steroid refractory syndromes.


REFERENCES