

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

Issue: *Neuroendocrine Immunology in Rheumatic Diseases***Anti-TNF therapy restores the hypothalamic-pituitary-adrenal axis**Fabiola Atzeni,¹ Rainer H. Straub,² Maurizio Cutolo,³ and Piercarlo Sarzi-Puttini¹¹Rheumatology Unit, University Hospital L. Sacco, Milan, Italy. ²Laboratory of Experimental Rheumatology and Neuroendocrino-Immunology, Department of Internal Medicine I, University Hospital Regensburg, Regensburg, Germany.³Division of Rheumatology, Department of Internal Medicine and Medical Specialities, University of Genoa, Genoa, Italy

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Tumor necrosis factor (TNF) inhibitors are associated with greater improvements in the symptoms and signs of rheumatoid arthritis (RA) and, more importantly, a lower risk of joint damage. TNF is an important mediator of the alterations in neuroendocrine axes characterizing RA. Long-term therapy with anti-TNF agents sensitizes the pituitary gland and improves adrenal androgen secretion, thus stimulating an alternative form of anti-inflammatory action.

Keywords: rheumatoid arthritis; cortisol; TNF inhibitors; hormones

Introduction

Tumor necrosis factor (TNF)- α is a proinflammatory cytokine that is produced by various cell types, including blood monocytes, macrophages, mast cells, and endothelial cells, and plays multiple complex functional roles within the immune system, including the stimulation of inflammation, cytotoxicity, the regulation of cell adhesion, and the induction of cachexia.^{1,2} It also indirectly downregulates inflammation by stimulating the pituitary release of corticotropin, which stimulates the adrenal cortex release of cortisol, a direct inhibitor of inflammation (see Fig. 1).³

The alterations in the hypothalamic-pituitary-adrenal (HPA) axis induced by chronic inflammatory diseases, such as rheumatoid arthritis (RA) include the inadequate spontaneous and stimulated secretion of cortisol, decreased secretion of adrenocorticotrophic hormone (ACTH), and a decrease in adrenal androgens.^{4,5}

TNF- α blockers not only improve the symptoms and signs of RA and, more importantly, reduce the risk of joint damage,⁶⁻⁸ but may also support other important anti-inflammatory pathways, such as the hormonal axes.⁹

Hypothalamic-pituitary-adrenal axis

In RA patients with high TNF levels, the serum levels of cortisol and ACTH are inadequate in relation to the level of inflammation. It is not known why these alterations occur, but continuous stimulation of the hypothalamus with TNF and interleukin (IL)-6 induces a hypothalamic-pituitary adaptation that leads to high cytokine and lower than normal hormone levels.⁴ The decrease in adrenal hormone levels is due to the direct inhibitory effect of TNF on the expression of the steroidogenic acute regulatory protein and the ACTH-stimulated expression of the steroidogenic enzymes P450ssc, P450c21, and P450c11 in adrenocortical cells.¹⁰ A recent study has shown that anti-TNF antibody injections rapidly and continuously increased ACTH and cortisol levels in prednisolone-naïve RA patients for a period of 12 weeks, thus indicating the normalization of the immune and neuroendocrine systems; furthermore, the ratio of serum cortisol to serum ACTH levels decreased during treatment, which suggests the sensitization of the pituitary gland.⁹ It has also been shown that the liver cell production of cortisol binding globulin (CBG) is low during inflammatory processes and does not change during anti-TNF treatment,¹¹ which means that the changes

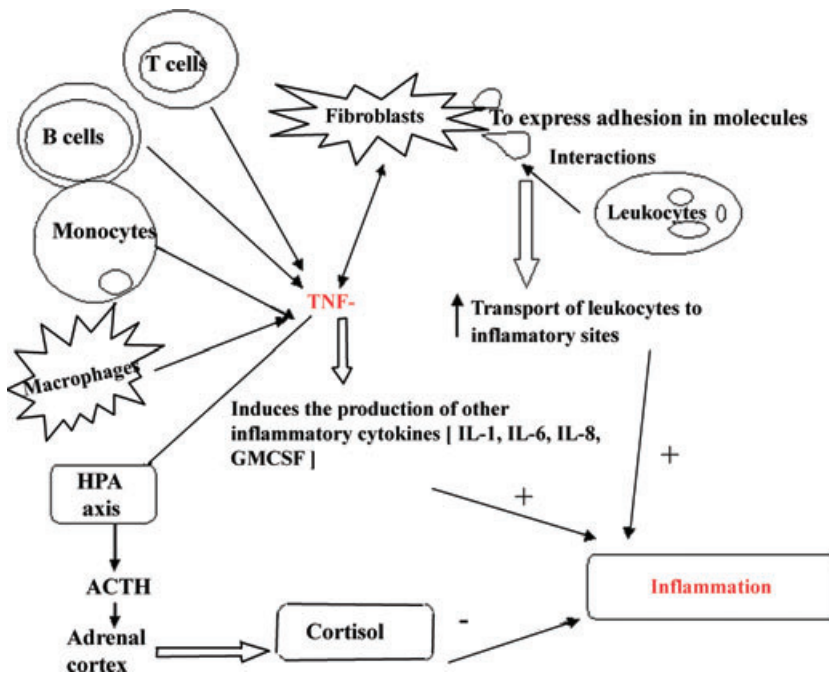


Figure 1. The roles of tumor necrosis factor-alpha.

in hormone concentrations induced by anti-TNF agents are not due to changes in serum CBG levels.

Long-term anti-TNF therapy therefore sensitizes the pituitary gland and improves adrenal androgen secretion in prednisolone-naïve patients. These signs of the normalization of the HPA axis indicate the additional anti-inflammatory effect of anti-TNF treatment in patients with RA. As TNF inhibits the adrenal conversion of 17-hydroxyprogesterone (17OHP) into cortisol, thus leading to low serum cortisol levels, we have recently investigated the role of HPA axis hormones and found that responders to TNF blockade have higher serum cortisols and show a rapid clinical improvement.¹² These findings indicate that some patients rapidly benefit from the use of anti-TNF agents probably as a result of the restoration of steroidogenic enzymes P450c21 and P450c11 in adrenocortical cells.

Furthermore, the results of an observational study have shown that an improvement in the disease activity score (DAS28) negatively correlated with baseline serum cortisol levels and the cortisol: ACTH ratio, thus demonstrating that simple cortisol and ACTH measurements can help guide anti-TNF treatment.¹³

Finally, although patients with psoriatic arthritis (PsA) treated with fully humanized, soluble dimeric fusion protein do not show any significant sensitization of the pituitary and adrenal glands, the ratios between the variations in serum cortisol and 17OHP levels and serum androstenedione (ASD) correlate with better clinical improvement after 12 weeks of etanercept treatment.¹⁴

Conclusions

The HPA axis is altered in chronic inflammatory diseases, such as RA and PsA. TNF is an important mediator of these alterations as it inhibits the expression of the steroidogenic acute regulatory protein and the ACTH-stimulated expression of steroidogenic enzymes P450ssc, P450c21, and P450c11 in adrenocortical cells.^{15,16} Long-term anti-TNF therefore restores the hormonal pathway, thus normalizing hormone levels and hormone ratios, and leading to a rapid clinical improvement.

Conflicts of interest

The authors declare no conflicts of interest.

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