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Anti-TNF antibody therapy does not change serum levels of cortisol binding globulin in patients with rheumatoid arthritis but it increased androstenedione relative to cortisol

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Keywords: Rheumatoid arthritis, adalimumab, cortisol binding globulin, cortisol, androstenedione

Running title: Anti-TNF and cortisol binding globulin in RA
Abstract

Objective: Cortisol binding globulin (CBG) is produced by liver cells and is inhibited by proinflammatory cytokines such as IL-6. CBG serum levels are typically low during prolonged inflammatory processes. Thus, observed changes of cortisol during anti-TNF therapy may be related to changes of CBG in RA. This study aimed at investigating the course of CBG during anti-TNF therapy in RA.

Methods: In this longitudinal study with subcutaneous adalimumab, 13 long-standing RA patients without prior prednisolone were included.

Results: Upon treatment with anti-TNF, we observed a strong decrease of clinical markers of inflammation and serum IL-6. Serum levels of cortisol, CBG, and the ratio of cortisol/CBG did not markedly change, whereas the ratio of serum CBG / IL-6 increased (p=0.004). In parallel, levels of ACTH decreased during the observation period. The ratio of the adrenal androgen androstenedione divided by serum cortisol increased during the observation period (p=0.036).

Conclusions: This study demonstrates relatively normal levels of CBG and a normal ratio of CBG / cortisol during anti-TNF therapy. Thus, earlier observed changes of cortisol in relation to IL-6 during anti-TNF therapy may not be related to changes of CBG. This study further confirmed some of our earlier data with infliximab in another cohort.

INTRODUCTION

In a chronic inflammatory disease such as rheumatoid arthritis (RA), the hypothalamic-pituitary-adrenal (HPA) axis demonstrates alterations: 1. It was demonstrated that patients have low spontaneous and stimulated cortisol secretion in relation to inflammation \(^7\). 2. Inadequate secretion of ACTH relative to inflammation was described \(^7\). 3. During a long-term inflammatory disease such as RA adrenal androgens decrease \(^8\)–\(^11\). Causes for these alterations are only partly understood but striking changes on all levels of the HPA axis seem to play a role. Cytokines such as IL-6 and TNF are likely to play a prominent role for these alterations.

In a German RA cohort, we recently demonstrated that long-term therapy with anti-TNF using infliximab sensitizes the pituitary gland and favors adrenal androgen secretion \(^12\). Since cortisol binding globulin (CBG) production may be inhibited by proinflammatory cytokines such as IL-6 \(^13\)–\(^14\), earlier observed changes of cortisol may be dependent on changes of CBG serum levels. This present study in RA patients during anti-TNF therapy aimed to investigate serum levels of CBG. As compared to the earlier study \(^12\), we used a completely different cohort from Italy using a different anti-TNF therapy with adalimumab (to demonstrate possible class effects of anti-TNF antibodies).

PATIENTS AND METHODS

Patients and blood samples

In this study with adalimumab (Abbot S.p.A., Campoverde di Aprilia, Italy), we included 13 Caucasian RA patients (all postmenopausal women) with RA fulfilling the ACR criteria for RA \(^15\). The patients were selected according to the inclusion criteria of the Adalimumab Research in Active RA study (ReAct). All patients did not receive parallel or prior (6 months before) prednisolone therapy. All patients were administered additional methotrexate (stable throughout this study) but no other immunosuppressive drugs (Table 1). Patients were assigned to receive single self-injections of adalimumab subcutaneously at 40 mg every other week. Efficacy assessments included ACR and EULAR response criteria (F.A., P.S.-P.). \(^16\) A baseline blood sample was taken 1 to 2 weeks before the start of adalimumab therapy. Anti-TNF antibodies were infused on week 0, 2, 4, 6, 8, 10, and 12. For this study, patients were clinically investigated and blood was drawn between 08:00 and 09:00 in the morning when the patients visited the outpatient clinic on the baseline day, week 2, 6, and 12. The blood was immediately centrifuged and serum was stored on – 80°C. The study was approved by the Ethics Committee of L. Sacco University Hospital, Italy.

Laboratory parameters. We used radioimmunometric assays for the quantitative determination of serum levels of CBG (Biosource, Nivelles, Belgium) and cortisol (Coulter Immunotech, Marseilles, France). Serum levels of IL-6 (high sensitivity Quantikine, R&D Systems, Minneapolis, MN, USA), androstenedione (ASD; IBL, Hamburg, Germany), and ACTH (Sangui BioTech, Inc., California, U.S.A.) were measured by immunometric enzyme immunoassays. Intraassay and interassay coefficients of variation for all tests were below 10%.

Statistical Analysis. Means between different time points during the course of anti-TNF therapy were compared by Wilcoxon signed rank test for paired data (SPSS/PC, Advanced Statistics, V11.5.1, SPSS Inc., Chi-
cago). A decrease or increase of a variable over time (during anti-TNF therapy) was tested by means of the non-parametrical Friedman test (SPSS). p < 0.05 was the significance level.

RESULTS

Anti-TNF therapy with adalimumab decreased swollen joint count (baseline vs. 12 weeks: 9.3 ± 0.6 vs. 2.9 ± 0.6, p=0.001), tender joint count (10.9 ± 0.9 vs. 6.5 ± 0.4, p=0.005), and serum levels of IL-6 (23.2 ± 8.9 vs. 3.2 ± 1.0, p=0.002).

Since cortisol determination may be influenced by presence of serum CBG, we measured this particular transport protein in this study. Baseline serum CBG was normal, and serum CBG did not markedly change during the therapy (Fig. 1A). Serum cortisol in relation to serum CBG did not change during anti-TNF therapy (Fig. 1B). The ratio of serum CBG / IL-6 significantly increased during the observation period (Fig. 1C).

Androstenedione is one of the major adrenal androgens. The ratio of serum androstenedione / cortisol increased during the observation period, which indicates that adrenal androgen secretion increases relative to cortisol secretion (Fig. 1E).

In addition, levels of ACTH decreased during 12 weeks of anti-TNF therapy (baseline vs. 12 weeks: 1.6 ± 0.1 vs. 1.2 ± 0.1 pmol/l, p=0.007) but cortisol remained relatively stable (615.3 ± 81.5 vs. 569.6 ± 77.1 nmol/l). We recently demonstrated that levels of hormones in relation to serum IL-6 can be used to estimate HPA axis activity in relation to this cytokine. This technique demonstrated that ACTH and cortisol serum levels increased relative to serum levels of IL-6 (ACTH: 0.46 ± 0.28 vs. 0.86 ± 0.24 pmol/l by pg/ml; cortisol: 62.1 ± 22.8 vs. 390.2 ± 108.1 nmol/l by pg/ml). This indicates that the main hormones of the HPA axis normalize relative to serum IL-6. With respect to ACTH (cortisol) serum levels are two (four) times higher in relation to IL-6 at 12 weeks compared to baseline.

DISCUSSION

CBG binds glucocorticoid hormones and regulates their biological disposal to target cells. CBG is mainly produced by the liver in all species examined. IL-6 and other proinflammatory cytokines can decrease production of CBG from liver cells. Thus, the proinflammatory load may decrease CBG serum concentrations in RA, which has been demonstrated in patients with prolonged critical illness on intensive care units. In this study, CBG baseline levels were normal in RA patients. Furthermore, CBG serum levels did not markedly change during the course of anti-TNF therapy. From these findings, we think that measurement of serum levels of cortisol are not markedly influenced by CBG concentrations in RA patients.

Beside the impressive improvement of clinical and laboratory parameters of inflammation, therapy with adalimumab decreased IL-6 secretion. IL-6 can be considered as hormone which announces the inflammatory status of peripheral joints to the adrenal gland and the central nervous system. It is important to mention that particularly the hypothalamic-pituitary axis undergoes desensitization upon repetitive IL-6 stimuli with a marked unresponsiveness of ACTH secretion. Removal of the IL-6 proinflammatory load by anti-TNF therapy leads to increased cortisol levels relative to IL-6. This phenomenon is probably not much influenced by CBG because this transport protein remains constant. This present study also demonstrated that ACTH serum levels decrease under anti-TNF therapy, which also shows that the proinflammatory load stimulates ACTH secretion. The improvement of hypothalamic-pituitary function can further be demonstrated when serum levels of ACTH are expressed relative to IL-6.

Earlier studies have delineated that adrenal androgen secretion is low in patients with RA. In our earlier study, we demonstrated relatively normal serum levels of androstenedione during the course of anti-TNF treatment. This was confirmed in this present study in Italian RA patients with another anti-TNF antibody. The relative preponderance of the glucocorticoid pathway (to cortisol) in relation to the androgen pathway (to androstenedione) was observed when using the ratio of serum cortisol / androstenedione. This particular ratio increased during anti-TNF therapy with infliximab, which was confirmed in this present study with adalimumab. These findings delineate that anti-TNF therapy favors androstenedione secretion relative to cortisol.

In conclusion, our present anti-TNF study with adalimumab in an Italian RA cohort demonstrated that CBG levels were not markedly altered during anti-TNF therapy. Thus, measurement of cortisol levels during anti-TNF therapy relative to serum levels of IL-6 are probably not influenced by CBG levels. Furthermore, we confirmed some of our recent findings in a German RA population using infliximab. Both studies demonstrated normalization of the HPA axis relative to IL-6 and an increase of adrenal androgens relative to cortisol. These positive effects must be considered as an additional systemic antiinflammatory influence of anti-TNF treatment in patients with RA.
Acknowledgments
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References


Table 1  Characteristics of patients and healthy subjects under investigation. Data are given as means ± SEM, percentages in parentheses, and ranges in brackets.

<table>
<thead>
<tr>
<th></th>
<th>RA patients</th>
</tr>
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<tbody>
<tr>
<td>Number</td>
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</tr>
<tr>
<td>Age (yr)</td>
<td>58.2 ± 2.4 [48 – 73]</td>
</tr>
<tr>
<td>Gender (f / m)</td>
<td>13 / 0</td>
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<tr>
<td>Disease duration (yr)</td>
<td>6.5 ± 1.8 (0.5 – 20)</td>
</tr>
<tr>
<td>Baseline erythrocyte sedimentation rate (mm 1st hour)</td>
<td>32.6 ± 5.5</td>
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<tr>
<td>Baseline C-reactive protein (mg / l)</td>
<td>143.4 ± 52.3</td>
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<tr>
<td>Baseline serum IL-6 (pg/ml)</td>
<td>23.2 ± 8.9</td>
</tr>
<tr>
<td>Positive for rheumatoid factor</td>
<td>13 (100)</td>
</tr>
<tr>
<td>Positive for antinuclear antibodies</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Baseline swollen joint score (points)</td>
<td>9.3 ± 0.6</td>
</tr>
<tr>
<td>Baseline tender joint score (points)</td>
<td>10.9 ± 0.9</td>
</tr>
<tr>
<td>Additional therapy</td>
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<tr>
<td>Prednisolone</td>
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<tr>
<td>Methotrexate</td>
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<td>Mean daily methotrexate (mg)</td>
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<tr>
<td>NSAID (COX1, COX2)</td>
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<tr>
<td>COX2 inhibitors</td>
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<td>Azathioprine</td>
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<tr>
<td>Sulfasalazine</td>
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FIGURE LEGENDS

Figure 1  Course of serum cortisol binding globulin (CBG) and androstenedione (ASD) in relation to cortisol during 12 weeks of anti-TNF antibody therapy in patients with rheumatoid arthritis. Baseline values are given as time point 0. The graph depicts serum CBG (A), the ratio serum cortisol/CBG (B), the ratio serum CBG/IL-6 (C), serum ASD (D), and the ratio serum ASD/cortisol (E). The data are given as means ± SEM. The p-value of the Friedman test is given. Abbreviations: IL-6, interleukin-6.
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