In etanercept-treated psoriatic arthritis patients clinical improvement correlated with an increase of serum cortisol relative to other adrenal hormones

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Abstract

Objective

In patients with rheumatoid arthritis (RA), long-term therapy with anti-tumor necrosis factor (TNF) antibodies sensitizes the pituitary gland and improves adrenal androgen secretion in prednisolone-naïve patients. However, whether this is similar in psoriatic arthritis (PsA) is not known. The aim of this study was to assess the effect of 12 weeks of etanercept treatment upon the function of the HPA axis in patients with PsA.

Methods

Eleven prednisolone-naïve patients (mean age 47.3 ± 8.9 years) with PsA were included. We measured serum levels of adrenocorticotropic hormone (ACTH), 17-hydroxyprogesterone (17OHP), cortisol, and androstenedione (ASD), at baseline and at 4 and 12 weeks after initiation of anti-TNF therapy (etanercept, 50 mg every week as a single dose by sc. injection). Clinical improvement was assessed using the Disease Activity Score – 28 (DAS-28).

Results

Mean levels of serum ACTH, serum cortisol, serum 17OHP and serum ASD did not markedly change during 12 weeks of etanercept treatment. Similarly, the ratio of serum cortisol divided by serum ACTH did not change during 12 weeks of anti-TNF treatment. However, an increase of serum cortisol relative to serum 17OHP or ASD was related to clinical improvement. This indicates that improvement was linked to higher serum cortisol levels relative to others adrenal hormones.

Conclusion

This is the first study to demonstrate baseline serum levels and the course of HPA axis-related hormones in patients with PsA. An increase of serum cortisol relative to others adrenocortical hormones (i.e., androstenedione and ACTH) was accompanied by clinical improvement.

Key words

Psoriatic arthritis, hormonal axes, anti-TNF agents, ACTH, cortisol.

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Introduction

Psoriatic arthritis (PsA) is an inflammatory disease that occurs in up to one third of patients with psoriasis and is usually diagnosed years after the appearance of psoriatic skin disease (1). PsA is a potentially debilitating disease that may affect entheses, small and large joints, and the axial skeleton. More than half of the patients with PsA exhibit progressive erosive arthritis, which often is associated with functional impairment (1). Several data support the role of proinflammatory cytokines in the pathophysiology of PsA and psoriasis such as tumor necrosis factor (TNF) and interleukin (IL)-6 (2, 3). TNF is a proinflammatory cytokine elevated in many inflammatory lesions, and its dysregulation characterizes many autoimmune diseases (4).

Similar to rheumatoid arthritis (RA), recent trials in PsA have shown excellent results with TNF blockers (etanercept, infliximab, and adalimumab), which have positive effects on the skin, on joints, on quality of life, on function, and they halt the disease progress as radiologically demonstrated (5, 6). Etanercept was the first approved TNF inhibitor for reducing signs and symptoms of PsA (5, 7, 8). Since TNF is a crucial cytokine interfering with neuroendocrine axes such as the hypothalamic-pituitary-adrenal (HPA) axis (9), its neutralization in PsA might also lead to a change of the hormonal milieu.

In a chronic inflammatory disease such as RA the alterations of the HPA axis are usually described as following: 1) the spontaneous and stimulated secretion of cortisol is inadequate relative to inflammation, 2) the secretion of adrenocorticotropic hormone (ACTH) is inadequate in relation to inflammation, and 3) adrenal androgens are decreased (9). However, these alterations have never been investigated in PsA. It was demonstrated that in patients with RA long-term therapy with anti-TNF monoclonal antibodies (infliximab and adalimumab) sensitizes the pituitary gland and improves adrenal androgen secretion in patients without previous prednisolone treatment (10). However, similar effects of anti-TNF therapy have never been shown in PsA. In a recent study in RA, it was demonstrated that TNF seems to inhibit the conversion of the cortisol precursor 17-hydroxyprogesterone (17OHP) into cortisol leading to low serum cortisol (11). In some patients, TNF neutralization increases serum cortisol and led to rapid clinical improvement probably by restoring this important metabolic step (11). However, this has never been studied in PsA.

The aim of this study in patients with PsA was to evaluate the effects of 12 weeks of etanercept treatment upon the function of the HPA axis. In addition, the behavior of HPA axis hormones was studied in relation to the clinical response.

Patients and methods

Patients

Eleven patients (7 women and 4 men; mean age at baseline 47.3 years [range 32 - 61]) with refractory PsA were include in this prospective cohort study. Baseline clinical and laboratory characteristics are given in Table I. The patients had severe erosive and destructive polyarthritis and two patients had also axial involvement. All patients fulfilled the classification criteria of the Psoriatic Arthritis Study Group (CASPAR) (12), and they were treated with methotrexate (mean dosage 10 mg[range 7.5-20 mg]) and etanercept (50 mg every week as a single dose by sc. injection). No patient received parallel glucocorticoid therapy.

During 12 weeks, clinical assessment included number of tender and swollen joints, duration of morning stiffness, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), and the Disease Activity Score including a 28-joint count (DAS-28). The DAS-28 score has been successfully used in patients with PsA (13). Psoriasis area and severity index (PASI) were also evaluated (Table I). Blood was drawn between 08:00 and 09:00 in the morning when the patients visited the outpatient clinic at baseline (screening evaluation), and at weeks 4 and 12. The blood was immediately centrifuged and serum was stored at -80°C.

Written informed consent was obtained from all patients and the study was

Table I. Baseline clinical and laboratory characteristics of psoriatic arthritis patients under study.

Number of patients	11
Age, yrs [range]	47.3 ± 8.9 [32-61]
Female / male, n (%)	4 / 7 (36.3 / 63.7)
Disease duration, yrs[range]	8.7 ± 4.3 [2-14]
Erythrocyte sedimentation rate, mm/1st hour	41.5 ± 11.6
C-reactive protein, mg/l	32 ± 12
Tender joint count, n	12.6 ± 2.8
Swollen joint count, n	8.7 ± 2.2
Joint pain, visual analog scale points	77.4 ± 4.9
Disease activity score – 28, pts	6.0 ± 0.4
Psoriasis area and severity index, pts	17.8 ± 13.9
Concomitant medication	
NSAIDs, n (%)	2 (18.2%)
Methotrexate, n (%)	9 (81.8%)
Cyclosporine A, n (%)	2 (18.2%)

Data are given as mean (SEM), percentages are given in parentheses, and ranges in brackets.

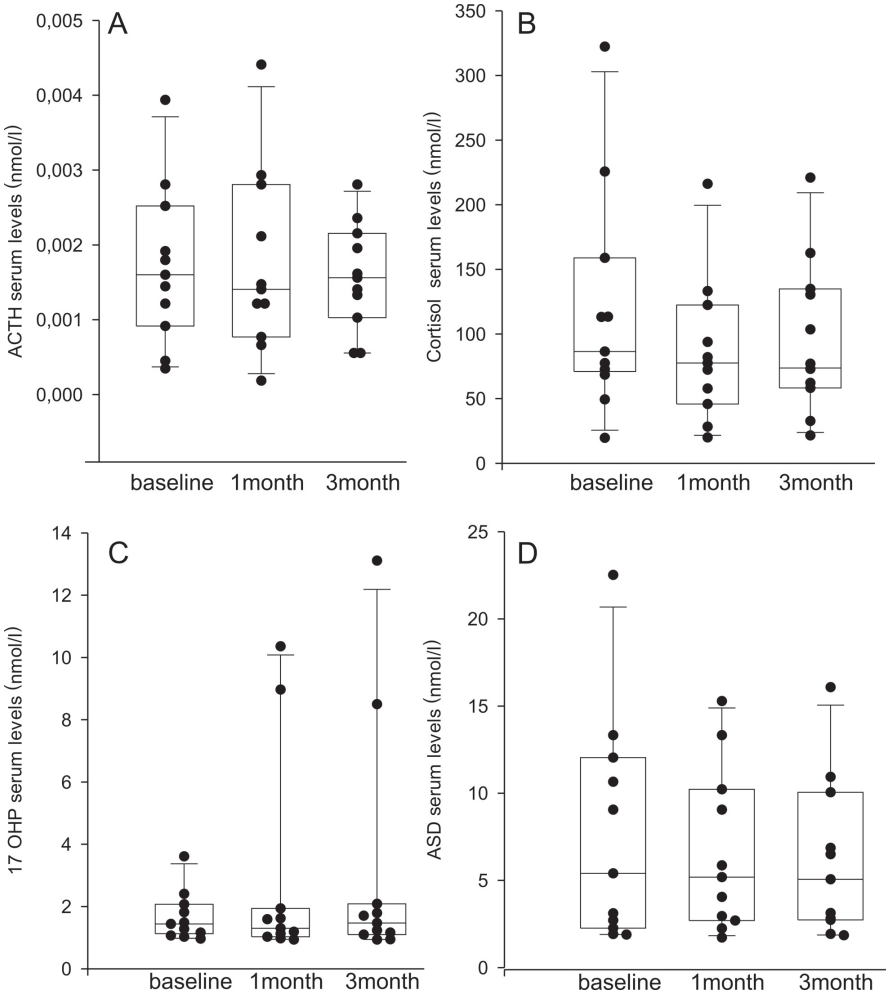

Fig. 1. Influence of 12 weeks of anti-TNF treatment with etanercept on serum levels of adrenocorticotropic hormone (ACTH) **(A),** cortisol **(B)**, 17-hydroxyprogesterone (17OHP) **(C)**, and serum androstenedione (ASD) **(D)**. All data are given as box plots with the 10th, 25th, 50th (median), 75th, and 90th percentile.

approved by the Research and Ethics Committee of the L. Sacco University Hospital, Milan, Italy.

Laboratory analysis

We used radioimmunometric assays for the quantitative detection of serum levels of cortisol (Coulter Immunotech, Marseilles, France; detection limit 10 nmol/l). Serum levels of 17OHP (IBL, Hamburg, Germany; detection limit 0.3 nmol/l), and serum levels of androstenedione (ASD, IBL; detection limit: 0.15 nmol/l) were measured by enzyme-linked immunosorbent assay (ELISA). Using a sensitive enzyme immunoassay for ACTH (Sangui Bio Tech, Inc., California, U.S.A., via IBL, Hamburg, Germany; detection limit: 0.1 pmol/l), we were able to determine a highly significant interrelation between ACTH measured in serum and ACTH assayed in plasma as reported in a previous study (11). In this present study, we evaluated ACTH in serum samples of PsA patients because no plasma samples were available.

Statistical analysis

Correlation analyses were performed with Spearman's rank correlation analysis (SPSS/PC, Advanced Statistics, Version 12.0; SPSS). Medians of different time points were compared by Wilcoxon signed rank test for paired data (SPSS). The lines in the figures are linear regression lines. A p value < 0.05 was the significance level.

Results

Clinical improvement

During the course of the study, the mean number of swollen joints (baseline 8.7 ± 2.2 *vs*. 3.2 ± 1.4 at 12 weeks; $p = 0.003$) and tender joints (baseline 12.6 ± 2.8 *vs*. 6.3 ± 2.5 at 12 weeks; $p < 0.01$), the PASI value (baseline 17.8 ± 13.9 *vs*. 12.1 ± 9.6 at 12 weeks; $p < 0.01$), the DAS-28 value (baseline 6.0 ± 0.4 *vs*. 4.5 ± 0.6 at 12 weeks; $p = 0.003$), and erythrocyte sedimentation rate (baseline 41.5 ± 11.6 *vs*. 22.05 ± 8.0 at 12 weeks; $p < 0.01$) decreased.

Changes of HPA axis hormones

In prednisolone-naïve patients with PsA, the mean levels of serum ACTH

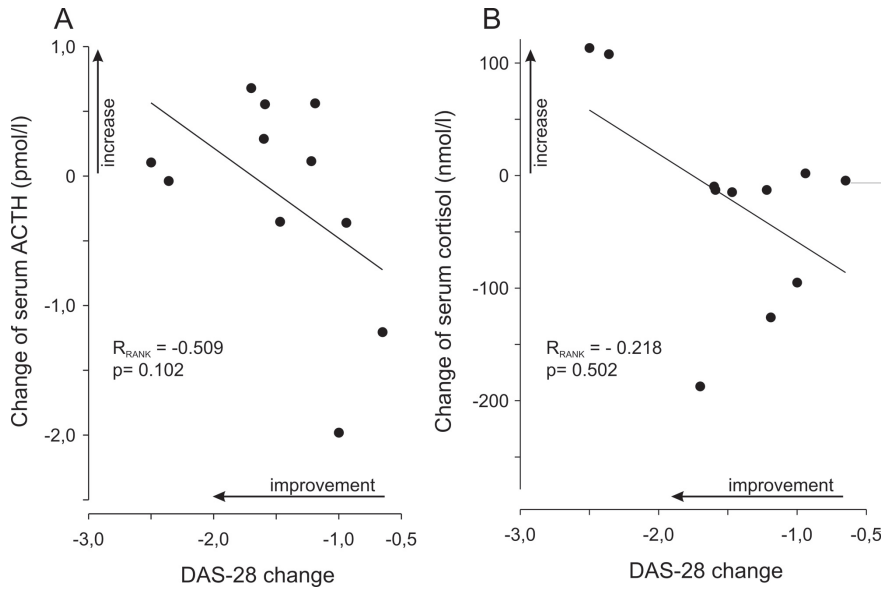

Fig. 2. Interrelation between DAS-28 improvement and change of serum adrenocorticotropic hormone (ACTH) and change of serum cortisol between baseline and 12 weeks (A and B).
DAS28 change = $DAS\text{-}28_{12\ weeks} - DAS\text{-}28_{baseline}$; change of ACTH = $ACTH_{12\ weeks} - ACTH_{baseline}$; change of cortisol = $cortisol_{12\ weeks} - cortisol_{baseline}$. An improvement of the DAS-28 is reflected by a negative value, and an increase of a serum hormone is displayed as a positive value. The diagrams show linear regression lines, Spearman's rank correlation coefficients (R_{RANK}), and the respective *p*-value.

and of serum cortisol did not markedly change after 4 and 12 weeks of etanercept therapy (Figs. 1A and 1B). Similarly, serum 17OHP and serum ASD did not markedly change over 12 weeks of anti-TNF treatment (Figs. 1C and 1D). In the presence of an elevated erythrocyte sedimentation rate and increased serum levels of C-reactive protein (Table I), baseline ACTH and cortisol are inadequately normal in relation to inflammation.

Change of DAS-28 in relation to change of ACTH or cortisol

Clinical improvement was calculated as a difference between DAS-28 at 12 weeks minus DAS-28 at baseline (called change of the DAS-28). A change of the DAS-28 was not related to a change of serum levels of ACTH (Fig. 2A) or cortisol (Fig. 2B). Although the change of DAS-28 and the change of serum hormones seem to be inversely related, this did not reach the significance level (Fig. 2).

Change of clinical improvement in relation to change of hormone ratios

A change of the DAS-28 was not related to a change of serum cortisol relative to serum ACTH (Fig. 3A). This indicates that the interplay between the pituitary and adrenal gland is not

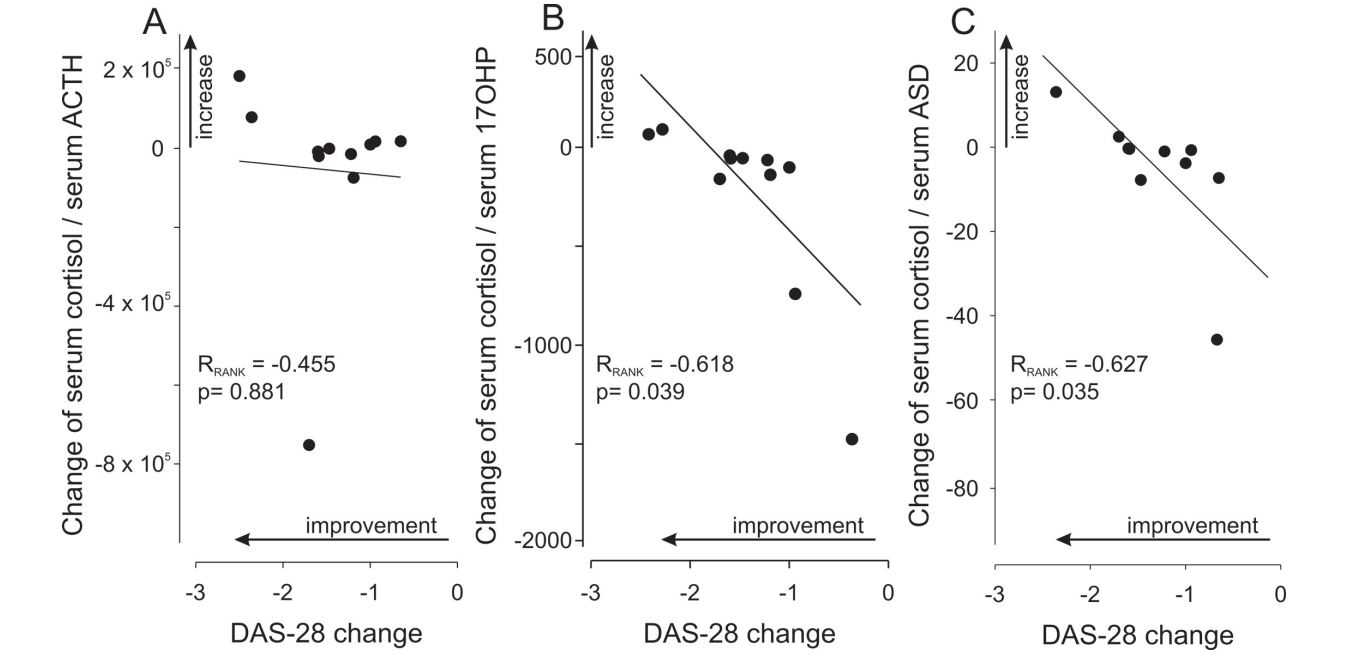

Fig. 3. Interrelation between clinical improvement and the change of the molar ratio of serum cortisol divided by serum adrenocorticotropic hormone (ACTH) **(A)**, serum cortisol divided by serum 17-hydroxyprogesterone (17OHP) **(B)**, and serum cortisol divided by androstenedione (ASD) **(C)** evaluated after 12 weeks of anti-TNF therapy.
DAS28 change = $DAS\text{-}28_{12\ weeks} - DAS\text{-}28_{baseline}$; change of Cort/ACTH = $Cort/ACTH_{12\ weeks} - Cort/ACTH_{baseline}$; change of Cort/17OHP = $Cort/17OHP_{12\ weeks}$ - $Cort/17OHP_{baseline}$; change of Cort/ASD = $Cort/ASD_{12\ weeks}$ - $Cort/ASD_{baseline}$. An improvement in DAS-28 is expressed as a negative value; and an increase of the ratio is reflected by positive values. An increase of the ratio appears if serum levels of cortisol (numerator) increase or serum levels of the hormone in the denominator decrease. Thus, an increase reflects the increase of cortisol relative to another hormone (means a preponderance of cortisol relative to the other hormone). The diagrams show linear regression lines, Spearman's rank correlation coefficients (R_{RANK}), and the respective *p*-value.

markedly changed during 12 weeks of anti-TNF therapy, whether the patients improved or not.

Importantly, a change of the DAS-28 (reflecting improvement) was related to increased serum levels of cortisol relative to the precursor 17OHP (Fig. 3B). A similar interrelation was observed between DAS-28 and the ratio of serum cortisol divided by serum ASD (Fig. 3C). This indicates that in PsA an anti-TNF therapy-induced improvement of the DAS-28 is related to an increased serum cortisol relative to 17OHP and the adrenal androgen ASD.

In addition, the change of number of swollen joints (week12 minus baseline reflecting improvement) was related to an increase of serum cortisol relative to the precursor 17OHP (R_{Rank}= -0.752, p = 0.008). A similar trend existed for the change of the number of tender joints and the increase of serum cortisol relative to the precursor 17OHP (R_{Rank} = -0.522, p = 0.090). However, a change of the erythrocyte sedimentation rate or the PASI value did not correlate with any changes of the ratios given in Figure 3.

Discussion

Psoriasis is a chronic skin disorder affecting approximately 1% to 3% of the world's population (14). A considerable proportion of patients with psoriasis will develop a form of inflammatory arthritis known as PsA (1). Significant advances have been made in pathophysiology research in PsA and psoriasis, with recent findings strongly implicating that T cells and inflammatory cytokines such as TNF play an important role (2, 3). The prevalence of arthritis in patients with psoriasis may be far higher than the previously accepted rate of 7% (15). In a recent study of 5795 members of the Nordic Psoriasis Association, the prevalence was found to be 30% (16). Due to the inefficiency of current disease-modifying antirheumatic drugs (DMARDs) and non-steroidal anti-inflammatory drugs (NSAIDs) in stopping the progression of PsA, biologicals have emerged as a hopeful alternative therapy in PsA (6, 17, 18). Two clinical trials have demonstrated that etanercept is generally safe, efficacious, and well-tolerated in PsA (6-8).

Recently, we described the sensitization of the pituitary gland in prednisolone-naïve patients with RA treated with anti-TNF agents, which was demonstrated as a rapid increase in the average ACTH serum concentration after every infusion of infliximab (10). In contrast, in this present study the mean levels of serum ACTH and of serum cortisol did not markedly change during anti-TNF therapy in prednisolone-naïve patients with PsA. This suggests a low or absent sensitization of the pituitary gland in this group of PsA patients compared to RA patients. Since PsA synovial explants produced more IL-1β, IL-2, IL-10, IFN-γ, and TNF than those of RA or osteoarthritis (19), we hypothesize that a low or absent sensitization of the HPA axis may be related to substantially higher levels of circulating cytokines in PsA compared to RA, and, in addition, a different mode of anti-TNF blockade might play an important role for the contrasting results (etanercept in PsA *vs*. infliximab / adalimumab in RA).

Serum 17OHP and serum ASD also did not markedly change over 12 weeks of etanercept treatment in these PsA patients. However, the change of the molar ratio of serum cortisol to serum 17OHP and the change of the molar ratio of serum cortisol to ASD were related to clinical improvement. The ratio of serum cortisol to serum 17OHP is a good estimate to evaluate the conversion of the cortisol precursor 17OHP into cortisol via the P450c21 and the P450c11, which can be blocked by TNF in adrenocortical cells (20). If cortisol increases relative to its precursor 17OHP under anti-TNF therapy with etanercept, the break from this conversion step might be removed resulting in increased serum cortisol relative to 17OHP. This only happens in patients with an improvement in DAS-28 (high negative value in Fig. 3). Those patients with no or only little improvement in DAS-28 demonstrated lower cortisol levels in relation to the precursor 17OHP. Similar findings have recently been described in RA patients under infliximab/adalimumab (11). It is further interesting that in PsA patients with strong improvement during etanercept therapy, serum levels of cortisol relative to ASD increased. This has not been studied in patients with RA. Since ASD is the most important precursor for androgens, this demonstrates an up-regulation of the cortisol pathway relative to the androgen pathway.

In conclusion, PsA patients under etanercept for 12 weeks demonstrate improvement of clinical arthritis, which is related to on increase of cortisol relative to 17OHP or ASD. It might well be that a preponderance of cortisol relative to 17OHP and adrenal androgen ASD is advantageous in PsA.

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