ARTHRITIS & RHEUMATISM
Vol. 58, No. 4, April 2008, pp 976–984
DOI 10.1002/art.23385

Increased Cortisol Relative to Adrenocorticotropic Hormone Predicts Improvement During Anti–Tumor Necrosis Factor Therapy in Rheumatoid Arthritis

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Objective. **Some patients with chronic inflammatory diseases such as rheumatoid arthritis (RA) improve rapidly from anti–tumor necrosis factor (anti-TNF) therapy. No sensitive markers are available that might predict outcome of anti-TNF therapy. We undertook this study to investigate the predictive value of hypothalamic–pituitary–adrenal (HPA) axis hormones for clinical improvement during anti-TNF therapy.**

Methods. **An observational study in 23 RA patients was followed by a validation study in 38 RA patients. The patients receiving anti-TNF antibodies had no glucocorticoid treatment, and we measured baseline serum levels of adrenocorticotropic hormone (ACTH) and cortisol. Improvement during anti-TNF antibody treatment was judged by the Disease Activity Score in 28 joints (DAS28), and serum levels of cortisol were measured at followup.**

Results. **The observational study demonstrated that improvement in the DAS28 correlated negatively with baseline serum levels of cortisol ($R = -0.520$, $P = 0.011$) and the cortisol:ACTH ratio ($R = -0.700$, $P = 0.0002$). In the longitudinal part of the study at followup, those patients with good improvement and initially low serum levels of cortisol demonstrated an increase of serum cortisol, in contrast to patients with little or no improvement. Findings in the observational study were supported by those in the validation study in a group of RA patients with less inflammation (correlation of improvement in the DAS28 with cortisol:ACTH ratio: $R = -0.320$, $P = 0.025$).**

Conclusion. **This is the first study in a human**

ISRCTN 68762628. FDA: BL 125057 (adalimumab portion of the studies).

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The observational study was supported by the respective institutions and by Centocor Inc., Malvern (now Horsham), PA, and Abbott SpA, Campoverde di Aprilia, Italy. The validation study in Amsterdam was funded by a Health Care Efficiency Research Program grant from the Netherlands Organization for Health Research and Development in assignment of the Netherlands Organization for Scientific Research (grant 945-02-029), the Dutch Arthritis Association, and the European Community's Sixth Framework Programme Autocure funding.

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Dr. Straub has received consulting fees and honoraria (less than $10,000) from Merck, Germany. Dr. Fleck has received speaking fees, honoraria, and travel grants (less than $10,000) from Abbott. Dr. Atzeni has received travel grants (less than $10,000) from Abbott. Dr. Kalden has received speaking fees, honoraria, and travel grants (less than $10,000 each) from Abbott and Centocor. Dr. Schölmerich has received consulting fees, speaking fees, and/or honoraria (less than $10,000) from Abbott. Dr. Lorenz has received consulting fees, speaking fees, and/or honoraria (less than $10,000 each) from Abbott, Centocor, Essex, Inc., Wyeth, Roche, Merck, Sharp, and Dohme, Bristol-Myers Squibb, Medac GmbH, and Pfizer and travel grants (less than $10,000 each) from Abbott and Centocor. Dr. Tak has received consulting fees, speaking fees, and/or honoraria (less than $10,000 each) from Amgen, Abbott, Centocor, Schering-Plough, and Wyeth. Dr. Sarzi-Puttini has received travel grants and an honorarium (less than $10,000) from Abbott.

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Submitted for publication May 12, 2007; accepted in revised form December 20, 2007.

chronic inflammatory disease to demonstrate that inflammation-induced TNF interferes with HPA axis integrity, which is linked to the disease outcome. These findings position the HPA axis centrally in the vicious circle of perpetuation of chronic inflammation.

Prediction of success during anti–tumor necrosis factor (anti-TNF) antibody therapy in chronic inflammatory diseases such as rheumatoid arthritis (RA) is of outstanding importance, because extremely high therapy costs might be avoided and treatment efficacy should be improved. Predictive parameters are useful for the clinician and for pharmaceutical companies in order to improve therapy in chronic longstanding inflammatory diseases. However, no predictive markers are currently available that might help to guide decision making before anti-TNF antibody treatment. Such a predictive parameter should be accessible and measurable. It is expected that an identified predictive marker for success of anti-TNF therapy might also play an important role in the pathophysiology of these diseases.

In recent years, the roles of hormones and the peripheral nervous system have been investigated in the pathophysiology of chronic inflammatory diseases such as RA (1). In an animal model of arthritis, seminal work at the beginning of the 1990s has positioned the hypothalamic–pituitary–adrenal (HPA) axis centrally in chronic inflammation (2). However, findings of those studies have never been confirmed in patients with RA. At present, it is still not known whether the HPA axis really plays a central role in the perpetuation of the chronic inflammatory process in RA. Although we recognize the important antiinflammatory and antierosive roles of endogenous glucocorticoids in RA (3–5), we do not exactly know whether a disease-related increase of circulating TNF via a deterioration of the HPA axis can add to the destructive process.

The role of circulating or locally produced TNF as a factor influencing the human HPA axis has recently been reviewed (6). TNF seems to be an important factor in establishing a milieu with inadequately low cortisol and adrenocorticotropic hormone (ACTH) secretion in relation to ongoing inflammation (6). However, it is not known whether TNF-induced inhibition of adrenal glands leading to inadequate cortisol levels has any impact on the chronic disease process.

The aim of this study was to investigate whether baseline levels of HPA axis hormones can predict improvement in RA. If such a hormone parameter exists, its alteration might shed light on the pathophysiologic roles of TNF and the HPA axis and how they interplay.

Table 1. Characteristics of the study subjects*

	RA patients	
	Study 1 (n = 23)	Study 2 (n = 38)
Age, mean ± SEM years	51.0 ± 2.8	50.9 ± 2.0
No. of women/no. of men (% women/% men)	20/3 (87/13)	30/8 (79/21)
DAS28 at baseline (points), mean ± SEM	5.8 ± 0.2†	5.4 ± 0.2
ESR at baseline, mean ± SEM mm/hour	35.0 ± 4.4‡	23.8 ± 3.0
IL-6 level at baseline, mean ± SEM pg/ml	27.6 ± 6.2§	15.2 ± 3.8
Medication, no. (%)		
Prednisolone	0	0
Infliximab	7	0
Adalimumab	16	38
Methotrexate	22	28
NSAIDs	21 (91)¶	24 (63)
Methotrexate dosage, mean ± SEM mg/day	10.5 ± 1.0#	18.6 ± 1.2
Duration of anti-TNF therapy, mean weeks	12	16

* There were 35 healthy subjects with a mean ± SEM age of 51.3 ± 2.4 years. Twenty-six of these subjects (74%) were women and 9 (26%) were men. RA = rheumatoid arthritis; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; IL-6 = interleukin-6; NSAIDs = nonsteroidal antiinflammatory drugs; anti-TNF = anti–tumor necrosis factor.
† $P = 0.065$ versus patients in study 2.
‡ $P = 0.036$ versus patients in study 2.
§ $P = 0.078$ versus patients in study 2.
¶ $P < 0.01$ versus patients in study 2.
# $P < 0.001$ versus patients in study 2.

PATIENTS AND METHODS

Patients and healthy controls. This study consisted of 2 independent arms. In an observational part (study 1), 23 white RA patients were treated either with infliximab (10 mg/kg per intravenous infusion on day 0 and at weeks 2, 6, and 10; n = 7 in Erlangen, Germany) or with adalimumab (40 mg per subcutaneous [SC] injection on day 0 and at weeks 2, 4, 6, 8, and 10; n = 16 in Milan, Italy). In a second, validation study (study 2), 38 white RA patients in Amsterdam, The Netherlands were treated with adalimumab (40 mg per SC injection on day 0 and at weeks 2, 4, 6, 8, 10, 12, and 14). All patients had longstanding RA fulfilling the 1987 revised criteria of the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) (7). Initially, these patients were included in multicenter, double-blind, placebo-controlled, randomized anti-TNF antibody studies (8,9). From those studies, clinical data and patient samples were available in order to retrospectively study aspects of the endocrine system. The characteristics of patients are shown in Table 1. The respective parts of the study involving infliximab and adalimumab were approved by the Ethics Committees of the University of Erlangen–Nuremberg, Erlangen, Germany, the University Hospital L. Sacco, Milan, Italy, and the Academic

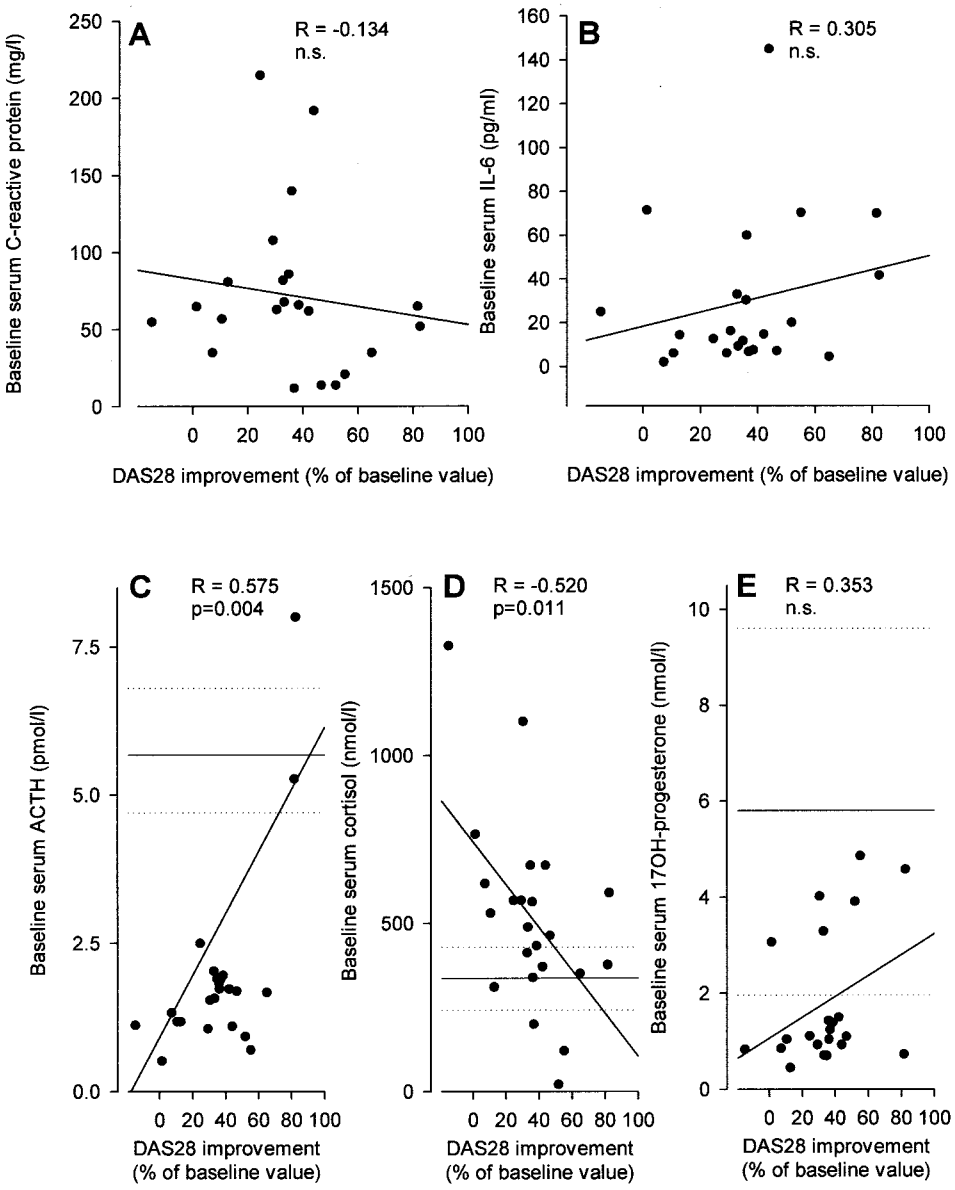

Figure 1. Interrelationship between clinical improvement during anti–tumor necrosis factor therapy and levels of inflammatory markers (**A** and **B**) or hormones (**C–E**) measured at baseline in the observational study (study 1). Graphs depict linear regression lines as well as Pearson correlation coefficients and their *P* values. In **C–E**, mean hormone levels of healthy subjects are represented by solid horizontal lines. Dotted horizontal lines represent the 95% confidence interval of the mean. NS = not significant; DAS28 = Disease Activity Score in 28 joints; IL-6 = interleukin-6; ACTH = adrenocorticotropic hormone; 17OH-progesterone = 17-hydroxyprogesterone.

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Clinical investigation, blood samples, and laboratory parameters. Clinical improvement was calculated according to the following formula: improvement (%) = 100 × (1 – [$DAS28_{followup}$/$DAS28_{baseline}$]), where DAS28 = Disease Activity Score in 28 joints (10). For both types of anti-TNF antibodies, detailed efficacy assessments including ACR and European League Against Rheumatism response criteria have been reported elsewhere, and they are not reported here (8,9).

Blood was obtained between 7:30 AM and 10:30 AM on day 0 and at followup. We used radioimmunometric assays for the quantitative determination of serum levels of cortisol (Coulter Immunotech, Marseilles, France). Serum levels of 17-hydroxyprogesterone (IBL, Hamburg, Germany) and serum levels of interleukin-6 (IL-6) (Quantikine; R&D Systems, Minneapolis, MN) were measured by enzyme-linked immunosorbent assay.

Using a sensitive enzyme immunoassay for ACTH (detection limit 0.1 pmole/liter; Sangui BioTech, Santa Ana,

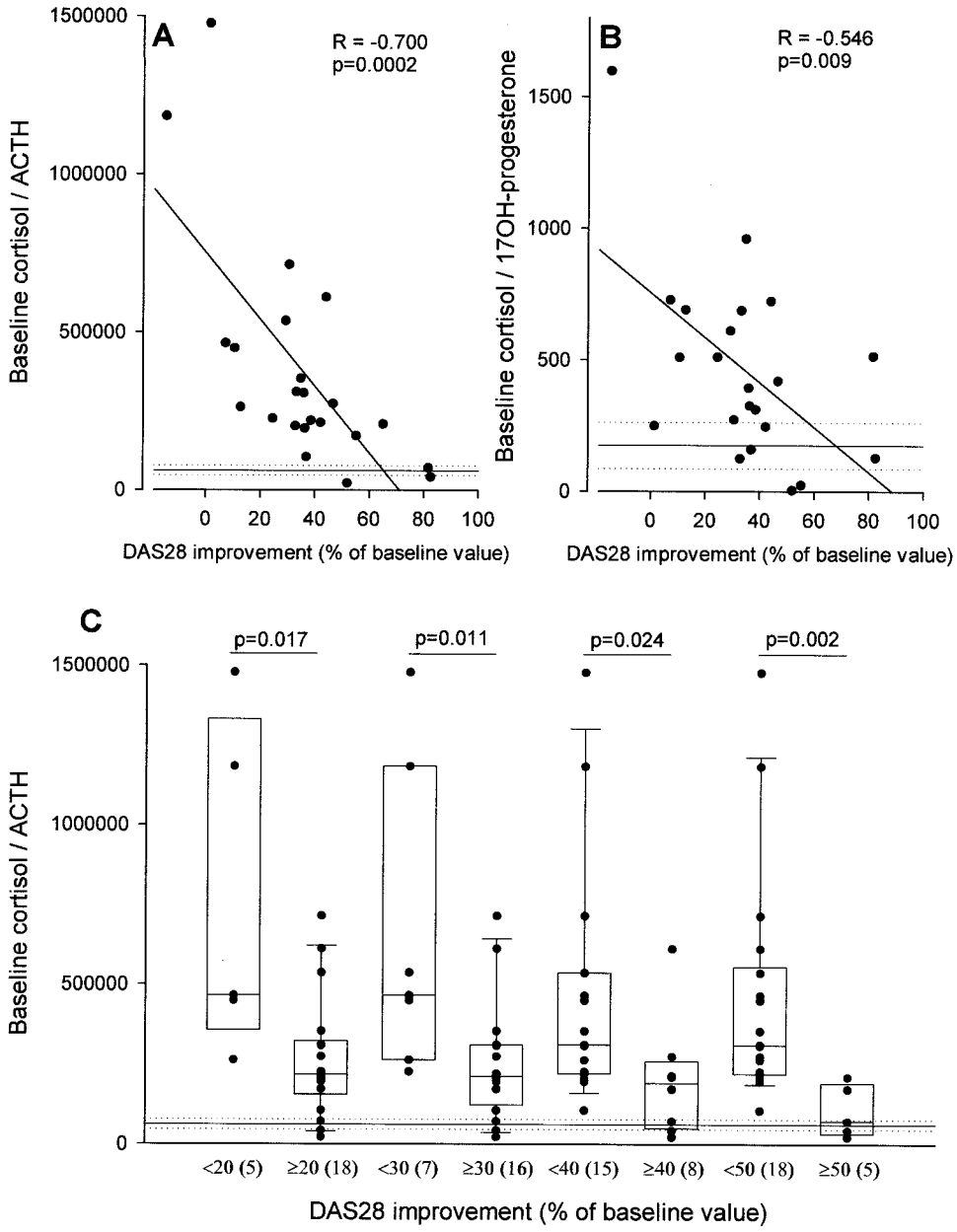

Figure 2. Interrelationship between clinical improvement during anti–tumor necrosis factor therapy and molar hormone ratios measured at baseline in the observational study (study 1). **A** and **B,** Molar ratio of serum cortisol:serum ACTH (**A**) and molar ratio of serum cortisol:serum 17-hydroxyprogesterone (**B**). Graphs depict linear regression lines as well as Pearson correlation coefficients and their *P* values. **C,** Box plots showing the interrelationship between clinical improvement and the molar ratio of serum cortisol:serum ACTH measured at baseline. Each box represents the 25th to 75th percentiles. Lines outside the boxes represent the 10th and the 90th percentiles. Lines inside the boxes represent the median. Values in parentheses are the number of patients in each group. Medians of nonresponders (improvement in the DAS28 <20%, <30%, <40%, and <50%) and responders (improvement in the DAS28 ≥20%, ≥30%, ≥40%, and ≥50%) were compared by *t*-test, and respective *P* values are shown. In all panels, mean molar ratios in healthy subjects are represented by solid horizontal lines. Dotted horizontal lines represent the 95% confidence interval of the mean. See Figure 1 for definitions.

CA, via IBL), we were able to demonstrate a highly significant interrelationship between ACTH measured in serum and ACTH assayed in plasma with the following regression equation: ACTH (plasma) = 7.2508 + 1.8707 × ACTH (serum) (R = 0.646, $P < 0.000001$; n = 112 healthy subjects) (11). In the present study, we measured ACTH in the serum samples

from healthy controls and patients with RA and reactive arthritis using this enzyme immunoassay. Intraassay and interassay coefficients of variation for all of the abovementioned tests were <10%.

Statistical analysis. Differences of group means were compared by *t*-test after investigation of variances in the 2 groups with the Levine test (SPSS/PC, Advanced Statistics, V15; SPSS, Chicago, IL). The interrelationship between 2 parameters was tested by Pearson correlation analysis (SPSS). In order to find a critical cutoff value for the ratio of serum cortisol:serum ACTH, which can predict clinical improvement using the DAS28, a receiver operating characteristic (ROC) analysis was carried out (SPSS). The ROC analysis provided the positive predictive value in order to predict the percentage of patients with clinical improvement (20%, 30%, 40%, and 50% improvement). *P* values less than 0.05 were considered significant.

As expected, the studied readout parameters in the observational study (study 1) did not differ significantly between the patient group receiving infliximab and the patient group receiving adalimumab. Thus, we did not further stratify the patient groups for statistical analyses in the observational study (study 1).

RESULTS

Observational study (study 1): baseline inflammatory markers and hormone levels in relation to clinical improvement. Neither baseline serum levels of C-reactive protein (CRP) nor baseline serum levels of IL-6 were related to clinical improvement (Figures 1A and B). In patients with good clinical improvement, baseline serum levels of ACTH were significantly higher compared with those in patients without improvement (Figure 1C). Baseline serum levels of ACTH were lower in RA patients than in healthy controls (Figure 1C). In contrast, patients with high improvement in the DAS28 during anti-TNF therapy had normal to low baseline levels of cortisol, whereas patients with little or no improvement demonstrated markedly higher baseline serum levels of cortisol (Figure 1D). Baseline serum levels of 17-hydroxyprogesterone were independent of clinical improvement and were somewhat lower than those in healthy subjects (Figure 1E).

The molar ratio of serum cortisol to serum ACTH was tightly regulated in healthy subjects (Figure 2A). This ratio measured at baseline was inversely related to clinical improvement at followup (Figure 2A). Those patients with good improvement demonstrated near-normal values, whereas patients without improvement or even worsening under anti-TNF therapy demonstrated a high molar ratio (Figure 2A). Similarly, the baseline molar ratio of serum cortisol to serum 17-hydroxyprogesterone was near normal in clinically improved patients and was higher in patients with little or no improvement (Figure 2B).

Observational study (study 1): prediction of clinical improvement by baseline levels of adrenal hormones. At each level of clinical improvement (from 20% to 50%), patients who responded to treatment (with clinical improvement ≥20%, ≥30%, ≥40%, and ≥50%) demonstrated a significantly lower molar ratio of serum cortisol to serum ACTH measured at baseline than did patients who did not respond to treatment (with clinical improvement <20%, <30%, <40%, and <50%, respectively) (Figure 2C). In order to determine a critical cutoff value for the ratio of baseline serum cortisol to baseline serum ACTH, which can distinguish between responders and nonresponders, an ROC analysis was performed. Depending on the degree of clinical improvement between 30%, 40%, and 50%, the cutoff values for the ratio were 450,000, 221,200, and 196,000, respectively. Using the respective cutoff value, one could distinguish responders from nonresponders with positive predictive values of 88%, 67%, and 80%, respectively (e.g., the chance is 80% that a patient with a baseline molar ratio <196,000 demonstrates a 50% improvement during anti-TNF therapy).

We hypothesized that neutralization of TNF increases endogenous cortisol secretion in patients with good response. It turned out that serum cortisol levels increased in patients with good improvement (>32% response rate), but they decreased in patients with little or no improvement (Figure 3A). Patients with initially low serum levels of cortisol and a marked cortisol increase during anti-TNF therapy demonstrated good improvement, in contrast to patients with initially high cortisol levels and cortisol decrease during followup of anti-TNF antibody treatment (Figure 3A). Improvement in the DAS28 correlated significantly with the change in serum cortisol level between baseline and followup (Figure 3B). A similar phenomenon was not observed with respect to the change in serum level of ACTH between baseline and followup (Figure 3C).

Validation study (study 2): prediction of clinical improvement by baseline levels of adrenal hormones. In the validation study (study 2), it turned out that improvement in the DAS28 was negatively correlated with the ratio of serum cortisol to serum ACTH (Figure 4A). Although this interrelationship was statistically significant, it was not as strong as that in the observational arm (compare with Figure 2A). However, patients in the observational arm had significantly greater inflammation at baseline compared with patients in the validation arm (Table 1).

In a further analysis, we combined data of patients in the 2 studies in order to investigate the combined predictive importance of the ratio of serum corti-

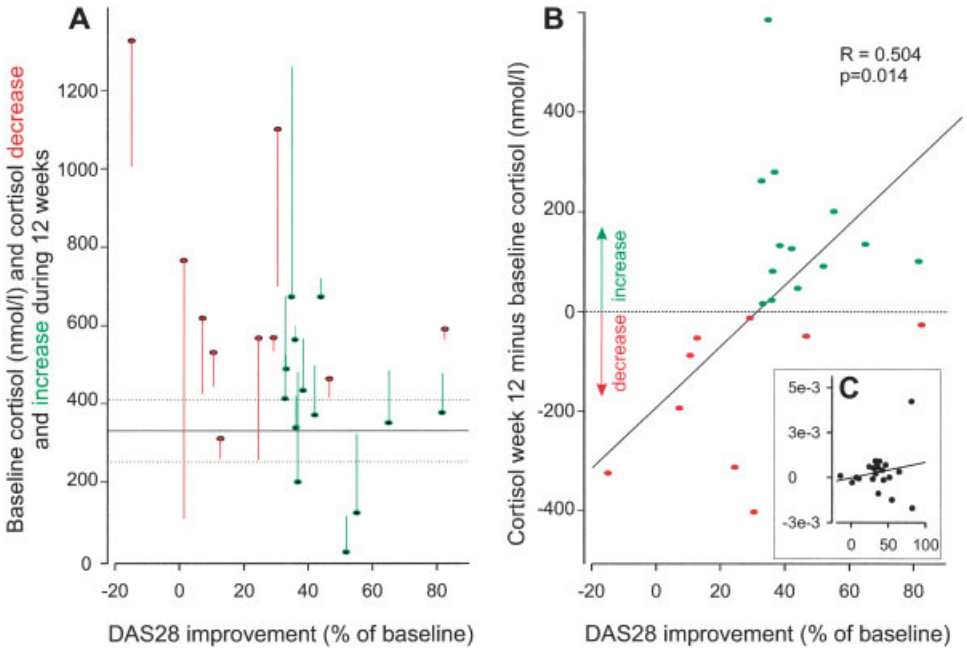

Figure 3. Course of serum cortisol in individual patients during anti–tumor necrosis factor therapy in the observational study (study 1). **A,** Baseline serum levels of cortisol, represented by colored circles, with colored lines indicating an increase (green) or decrease (red) between baseline and followup. Mean serum levels of healthy subjects are represented by solid horizontal lines. Dotted horizontal lines represent the 95% confidence interval of the mean. **B,** Interrelationship between improvement in the DAS28 and change in serum level of cortisol between baseline and followup. The graph depicts the linear regression line as well as the Pearson correlation coefficient and its *P* value. Dotted horizontal line indicates no change (no increase or decrease) in cortisol level. **C,** Interrelationship between improvement in the DAS28 and change in serum level of ACTH between baseline and followup (there was no significant change). See Figure 1 for definitions.

sol to serum ACTH (Figure 4B).This particular ratio correlated negatively with improvement in the DAS28 (Figure 4B). In addition, patients with initially low serum levels of cortisol and cortisol increase during anti-TNF therapy demonstrated good improvement, in contrast to patients with initially high cortisol levels and

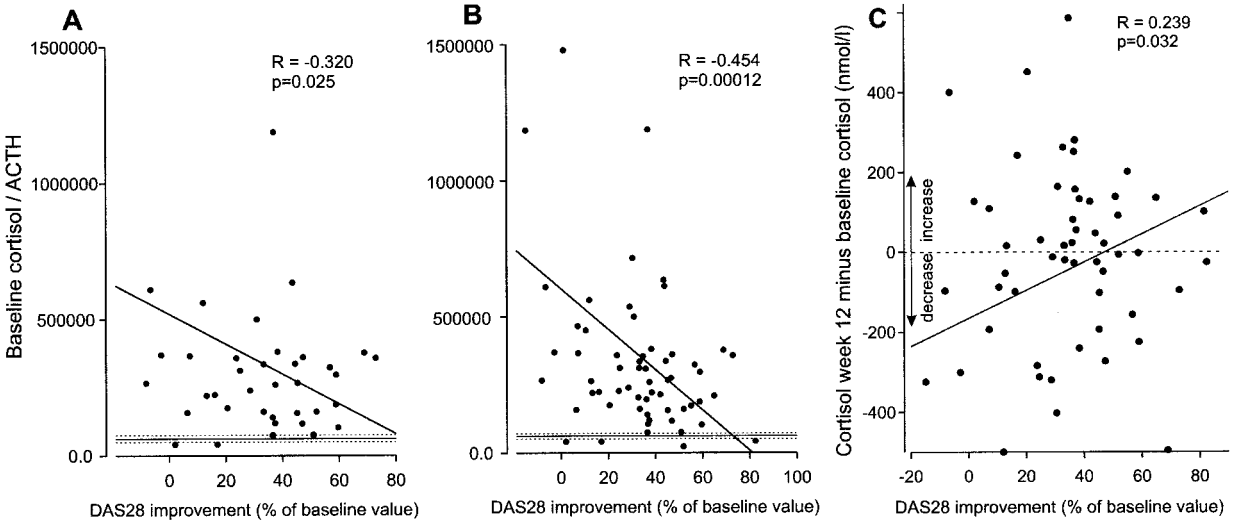

Figure 4. Interrelationship between clinical improvement during anti–tumor necrosis factor (anti-TNF) therapy and hormonal changes. **A,** Molar ratio of serum cortisol:serum ACTH in the validation study (study 2). **B,** Molar ratio of serum cortisol:serum ACTH in all patients in studies 1 and 2. In **A** and **B,** mean molar ratios in healthy subjects are represented by solid horizontal lines. Dotted horizontal lines represent the 95% confidence interval of the mean. **C,** Course of serum cortisol in individual patients during anti-TNF therapy in all patients with rheumatoid arthritis in studies 1 and 2. Dotted horizontal line indicates no change (no increase or decrease) in cortisol level. Graphs depict linear regression lines as well as Pearson correlation coefficients and their *P* values. See Figure 1 for other definitions.

cortisol decrease during anti-TNF antibody treatment (Figure 4C).

In order to determine a critical cutoff value for the ratio of baseline serum cortisol to baseline serum ACTH, which can distinguish between responders and nonresponders, an ROC analysis was performed for the combined data of study 1 and study 2. Depending on the degree of clinical improvement between 30%, 40%, and 50%, the cutoff values were 449,915, 380,916, and 214,451, respectively. Using these cutoff values, one could distinguish responders from nonresponders with positive predictive values of 62%, 86%, and 90%, respectively.

DISCUSSION

This is the first study to demonstrate an important relationship between the baseline status of HPA axis hormones as predictive parameters and clinical improvement resulting from anti-TNF therapy in RA patients. It turned out that a low ratio of baseline serum cortisol to baseline serum ACTH (a marker of HPA axis function) could reliably predict clinical improvement. The findings of this study position the HPA axis, particularly the adrenal glands, centrally in RA pathophysiology. Thus, our findings confirm the central role of the HPA axis in RA as studied in a rat model of arthritis (2).

Assuming that an inflammatory process usually up-regulates HPA axis function, cortisol levels are inappropriately normal in RA when cytokine levels are highly increased (12–14). Secretion of cortisol and ACTH is inadequately low in relation to serum levels of proinflammatory cytokines such as IL-6 and TNF (15). Only recently, the possibility of neutralizing distinct proinflammatory cytokines such as TNF and IL-6 demonstrated that these therapies can improve altered hormonal axes (6). TNF affects several important hormone-converting enzymes in adrenocortical cells such as P450scc, P450c17, and P450c21 (16,17). Thus, it seems obvious that TNF interferes with normal integrity of the HPA axis. However, it remains an open question whether TNF-induced deterioration of the HPA axis has any meaning for the ongoing inflammatory process and for disease outcome.

Since this study demonstrated that RA patients with low to normal serum levels of cortisol in relationship to ACTH particularly respond to anti-TNF therapy, which is accompanied by an increase of endogenous cortisol, TNF-induced deterioration of adrenal function most probably has an important effect on the disease process. The molar ratio of serum cortisol to serum ACTH is a marker of HPA axis function and integrity.

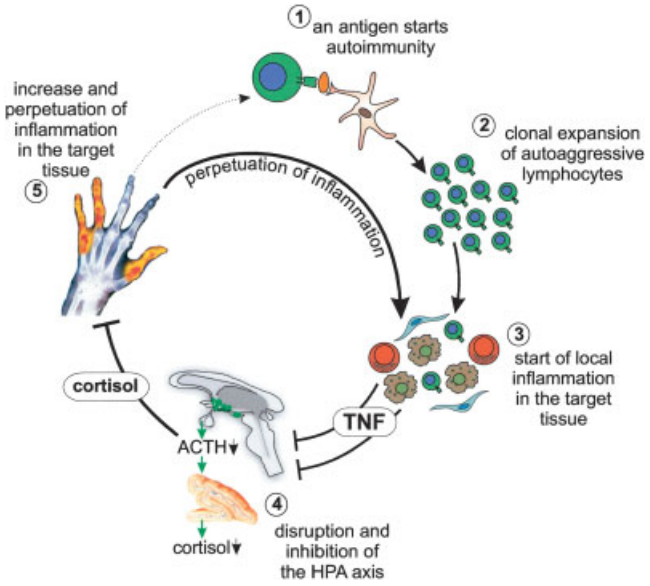

Figure 5. Position of the hypothalamic–pituitary–adrenal (HPA) axis in the pathophysiology of chronic inflammatory rheumatoid arthritis in relation to tumor necrosis factor (TNF) and local joint inflammation. A double vicious circle is demonstrated: 1) The disease is most probably started by a shift of balance from the tolerant to the aggressive side of an autoimmune response against a harmless antigen. 2) The immune response leads to clonal extension of T and/or B lymphocytes with an autoaggressive phenotype. 3) These autoaggressive cells start local tissue inflammation, which involves cell types such as macrophages, fibroblasts, natural killer cells, and many others. Local inflammation leads to spillover of TNF into the systemic circulation. 4) A longstanding increase of circulating TNF inhibits the entire HPA axis on several organ levels. Interestingly, serum cortisol levels are somewhat increased, whereas adrenocorticotropic hormone (ACTH) levels are significantly decreased. Nevertheless, the amount of cortisol is inadequate in relation to ongoing inflammation. 5) Endogenous cortisol would normally inhibit peripheral inflammation in the joints and elsewhere. Since cortisol levels are inadequate, inhibition of inflammation is insufficient. Insufficient suppression of inflammation perpetuates the disease process. Some patients with lower baseline serum levels of cortisol demonstrate good clinical response and elevation of serum cortisol under anti-TNF therapy. In this group of good responders, the TNF-induced brake on the HPA axis seems to be particularly strong.

This ratio is tightly controlled under normal conditions in healthy subjects. However, in patients with RA, this ratio largely increases as a result of inadequate regulatory interactions of the hypothalamic–pituitary axis and the adrenal glands. It seems as if the adrenal glands are uncoupled from the hypothalamic–pituitary axis, leading to normal to somewhat elevated cortisol levels but low ACTH levels. The reason for this discrepancy might be found in an activation of the adrenal gland independent of ACTH (17). Cytokines such as IL-6 are able to directly stimulate the adrenal glands (17). This might

lead to the observed increase of cortisol and low levels of ACTH, resulting in an increased cortisol:ACTH ratio.

Furthermore, this study distinguishes 2 groups of RA patients. The first group had relatively low baseline serum levels of cortisol and a near-normal molar ratio of cortisol to ACTH (on the right end of the x-axis in Figure 2A). These patients were good responders and their cortisol levels increased during anti-TNF therapy (the green dots in Figure 3). The second group of patients demonstrated high cortisol levels at baseline and a high ratio of serum cortisol to serum ACTH (on the left end of the x-axis in Figure 2A). This group of patients showed a decrease of endogenous cortisol during anti-TNF antibody treatment (the red dots in Figure 3).

At present, it is unclear why 2 types of RA patients exist. It might be speculated that the TNF influence on the HPA axis is remarkably different in the 2 groups. In one group (the nonresponders), TNF seems to stimulate endogenous cortisol, and TNF neutralization leads to a decrease of serum cortisol, which is related to a lack of improvement in the DAS28. In the other group (the responders), TNF seems to inhibit adrenal cortisol secretion, and TNF neutralization leads to an increase of serum cortisol, which is related to improvement in the DAS28. It might be that genetic prerequisites of TNF signaling or TNF-induced modulation of hormone conversion enzymes and cofactors might be critically different in responders compared with nonresponders. Further studies are needed to investigate this important possibility. The present study further demonstrates that the HPA axis has an important intermediate position in the vicious circle of RA pathophysiology (Figure 5).

In the comparison between the observational arm (study 1) and the validation arm (study 2), it is obvious that study 1 demonstrated a better predictive role of the serum cortisol:serum ACTH ratio than did study 2. Patients in study 2 had markedly less systemic inflammation (as indicated by lower erythrocyte sedimentation rate [ESR] and lower serum level of IL-6), which might have been due to stricter control of disease with methotrexate (a significantly higher dosage) (Table 1). Since methotrexate can inhibit secretion of TNF, it might well be that patients in study 2 had lower circulating levels of TNF compared with patients in study 1 (TNF levels were not measured due to interference from injected anti-TNF antibodies). Although anti-TNF therapy might inhibit TNF effects locally in the joint, the influence of this therapy on the adrenal level might be less marked due to lower circulating TNF levels. It needs to be determined whether the initial proinflammatory status as measured by ESR or other circulating markers of inflammation can even improve prediction of success of anti-TNF therapy.

In conclusion, in RA patients receiving anti-TNF therapy, low baseline serum levels of cortisol and low baseline cortisol levels in relation to ACTH predict clinical improvement. It is likely that an anti-TNF–mediated increase of serum cortisol plays an important role in this phenomenon. The present study demonstrated that a simple cortisol and ACTH measurement can help to further guide anti-TNF antibody treatment. This is particularly relevant because important parameters such as CRP level, ESR, and swollen joint count are not predictive in RA patients treated with anti-TNF antibodies plus methotrexate (18). We suggest that inclusion of cortisol and ACTH and their respective molar ratio in the decision-making process can help to determine the appropriateness of anti-TNF therapy in patients with RA.

AUTHOR CONTRIBUTIONS

Dr. Straub had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Straub.

Acquisition of data. Wijbrandts, Baeten, Atzeni, Grunke, Kalden, Lorenz, Tak, Sarzi-Puttini.

Analysis and interpretation of data. Straub, Pongratz, Cutolo, Wijbrandts, Baeten, Fleck, Atzeni, Grunke, Kalden, Schölmerich, Lorenz, Tak, Sarzi-Puttini.

Manuscript preparation. Straub, Pongratz, Cutolo, Wijbrandts, Baeten, Fleck, Atzeni, Grunke, Kalden, Schölmerich, Lorenz, Tak, Sarzi-Puttini.

Statistical analysis. Straub.

ROLE OF THE STUDY SPONSOR

In both studies (observational and validation), the original study design was independent of the present investigation because there existed no primary interest in hormonal analyses. The companies and research institutes carried out these earlier studies in order to test the beneficial effects of anti-TNF antibodies, and results of these studies have been published. Thus, the design of the present work was planned and carried out independently of pharmaceutical companies, and clinical data required for the current analyses were collected in the abovementioned study centers independent of companies. Funding of consumables and laboratory work for the present study was obtained from the University Hospital Regensburg independently of pharmaceutical companies. In addition, the pharmaceutical companies were not involved in data analysis and writing of the manuscript. The corresponding author had final responsibility for the decision to submit the manuscript for publication.

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