Glucocorticoid treatment in rheumatoid arthritis: low-dose therapy does not reduce responsiveness to higher doses

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ABSTRACT

Background. *Despite low-dose glucocorticoid (GC) treatment, many patients with rheumatoid arthritis (RA) require additional flare therapy with GC at higher doses. Since low dose GC has been suggested to confer resistance to higher doses, we aimed to assess if resistance was detectable on the clinical level in patients with active RA.*

Methods. *Eighty-nine patients with active RA (Disease Activity Score 28, DAS28 > 3.2; mean age 54.5 years, mean duration of RA 9.7 years) were consecutively enrolled into a one-week trial of a total of 250 mg prednisolone. We compared improvement of the DAS28 and the Simplified Disease Activity Index (SDAI) in groups of patients with (n = 41) and without (n = 48) low-dose GC at baseline (by t-test). In addition, we analyzed changes of all individual core set measures of disease activity using multivariate statistics.*

Results. *All clinical, serological and functional measures improved significantly over one week (p < 0.001). Baseline RA activity of patients with and without low-dose GC was on average ± standard deviation similar among the two groups (DAS28: 4.8 ± 1.2 and 4.9 ± 1.1; mean SDAI: 26.1 ± 14.0 and 25.9 ± 13.0, respectively), and likewise there was no difference between the two groups in the final disease activity reached, for both the DAS28 (1.4 ± 1.1 vs. 1.1 ± 1.0; p = 0.14) and the SDAI (11.1 ± 13.4 vs. 11.1 ± 11.4; p = 0.99). Improvement in all individual measures was also not different using a multivariate model (p = 0.26).*

Conclusion. *Pre-treatment with low-dose GC does not appear to portend GC resistance at least clinically, since the responsiveness to GC boosts is unaffected.*

Introduction

Treatment of rheumatoid arthritis is primarily based on the use of disease modifying antirheumatic drugs (DMARDs). These drugs have been shown to modulate the disease process, reduce signs and symptoms of RA, and retard radiographic progression and functional decline (1-3). In recent years, the concept of rapid and continued control of the disease process has become a mainstay of RA therapy (4, 5). Since the effectiveness of DMARDs usually has a delayed onset of 1-3 months during which active disease continues to prevail, glucocorticoids (GC) are frequently applied as "bridging therapy" at high or low doses to modulate disease activity (6); moreover, DMARDs, even if effective, are often associated with residual clinical activity, and therefore GC are also frequently used alongside established DMARD treatment as long term low-dose therapy (7-11). Low-dose GC (usually prednisone ≤ 15mg/d) has also been shown to significantly reduce progression of RA both as monotherapy and when employed in combination with DMARDs (12-16), and likewise high dose GC appear to be instrumental in interfering with the long-term disease process when employed together with DMARDs (17).

It is currently unknown if preceding low-dose GC therapy affects responsiveness to subsequent use of higher GC doses. This question is of particular importance since low-dose GC have been reported to lead to significant down regulation of the GC receptor (18, 19), suggesting the possibility of GC resistance. Consequently, GC resistance might reduce the effects of short-term GC dose increases in patients who have active disease despite low-dose GC therapy.

In the present study, we therefore addressed the question whether the response to higher doses of GC is reduced in RA patients with active disease who receive low-dose GC compared to those patients without current low-dose GC therapy.

Methods

Patients and study intervention

In the BELIRA trial ("Best Life In Rheumatoid Arthritis") patients with RA classified according to the American College of Rheumatology (ACR) criteria (20) received a total of 250 mg prednisolone over one week starting at 50 mg per day from day 1 to day 3, followed by 25 mg per day from day 4 to day 7 (21, 22). All patients also received proton pump inhibitors and calcium/vitamin D and were assessed at baseline and after one week. All subjects gave their written consent. Patients had to

have active disease at baseline with a Disease Activity Score 28 (DAS28) > 3.2 indicating at least moderate disease activity (23). Patients were allowed to have any concomitant DMARD therapy, and they were also allowed to have low-dose prednisone treatment of ≤ 15mg/d. All pre-study medications were continued, except for the low-dose GC which was replaced by the higher dose upon entry into the study. Exclusion criteria comprised acute infections, diabetes mellitus, hypertension, heart failure and pregnancy. The study was an open-label assessor-blinded investigation, similar to other recent prospective observational trials (5, 24). We identified 41 patients with and 48 patients without low-dose GC treatment at baseline.

Outcome measures

The primary endpoint in the BELIRA trial was the improvement of the DAS28. Secondary endpoints were improvement in two additional composite scores, the Simplified Disease Activity Index (SDAI) (25) and the Clinical Disease Activity Index (CDAI) (26), as well as individual variables, namely erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), swollen joint counts (SJ) and tender joint counts (TJ) based on 28 assessed joints, patient pain on a 100 mm visual analogue scale (VAS) (27), and patient and evaluator global assessment of disease activity (PGA, EGA) on a VAS.

Statistical analyses

We used *t*-tests to assess differences in the primary outcome. Power calculation for the primary endpoint indicated that a sample of 40 individuals in each group would allow the detection of a reduction in DAS28 > 0.6 at a power of 80% and an alpha level of 0.05. In addition to the composite index utilized for the primary endpoint (change in DAS28), we also employed a multivariate regression model using TJ, SJ, CRP, ESR, PGA, EGA as the dependent variables, and the presence or absence of low-dose steroids as the independent variable.

Finally, we evaluated potential effects of different pre-trial GC doses on changes of the DAS28 and the SDAI. We therefore correlated DAS28 and SDAI responses and GC dose (using Spearman correlation). Likewise we investigated whether cumulative GC doses at baseline were associated with DAS28 and SDAI responses to subsequent intermediate dose GC treatment.

Results

Patients

Eighty-nine patients with RA were enrolled in this trial. Their mean age was 54.5 ± 12.0 years, and 78 (87.6%) were female. The mean duration of RA was 9.7 ± 6.8 years. Forty-eight (53.8%) of these patients did not receive GC at baseline, and among the remaining 41 (46.2%) patients the dose of baseline prednisolone treatment ranged from 2.5 to 12.5 mg daily (mean dose 6.5 ± 2.4). The mean duration of baseline GC treatment in these patients was 32.7 ± 36.9 months (range: 2 to 129 months). Concomitant treatment consisted of one or more DMARDs (92%, mainly methotrexate), non-steroidal anti-inflammatory drugs (73%, mainly diclofenac or celecoxib) and analgesic drugs (9%; all tramadol). All these pre-study medications were continued at the pre-study doses during the one-week trial, except for the low-dose steroids, which were discontinued and replaced by the intermediate dose GC. Baseline characteristics of patients with and without prior low-dose GC therapy were similar (Table I).

Improvement of disease activity

All clinical, serological and functional measures indicated in Table I improved highly significantly after one week of intermediate dose GC therapy ($p > 0.001$ for all, detailed data not shown). When comparing the patient groups with and without preceding low-dose GCs, there was no significant difference in DAS28 improvement at the end of the one-week GC boost (1.1 ± 1.0 *vs.* 1.4 ± 1.1, respectively, $p = 0.14$; Table II). The improvement of the SDAI was virtually identical in both groups (11.1 ± 11.4 *vs.* 11.1 ± 13.4, respectively; $p = 0.99$; Table II), as was that of the CDAI.

When looking at the clinical and serological measures, there were small numeric differences in improvement between the two groups (Table II). Also, the directions of these differences among the two groups were not the same for many variables, indicating that any differences were due to chance rather than systematic consequences of disparities between the groups. In fact, a multivariate regression model confirmed this interpretation, since it also showed no difference of these meas-

Table I. Patient characteristics at baseline*.

	No glucocorticoids (n = 48)	Low-dose glucocorticoids (n = 41)	*p*-value
Age, years	53.6 ± 11.9	54.6 ± 12.2	0.69
Gender, % female	85.4%	90.2%	0.49
Mean disease duration, years	9.9 ± 6.7	8.1 ± 6.8	0.21
Rheumatoid factor, % positive	66.7%	78.0%	0.23
Number of previous DMARDs	1.98 ± 2.24	2.34 ± 2.05	0.43
DMARD use (%)	91.7%	92.7%	0.86
Methotrexate	50.0%	43.9%	0.57
Sulfasalazine	4.2%	7.3%	0.53
Other DMARDs	37.5%	41.5%	0.86
Duration of low-dose steroid treatment, months	-	32.7 ± 36.9	-
Disease Activity Score (DAS28)	4.9 ± 1.1	4.8 ± 1.2	0.64
Simplified Disease Activity Index (SDAI)	26.1 ± 14.0	25.9 ± 12.9	0.95
Clinical Disease Activity Index (CDAI)	24.2 ± 13.1	23.6 ± 11.9	0.81
Swollen joint count, 0-28	7.7 ± 5.9	7.5 ± 5.5	0.93
Tender joint count, 0-28	7.5 ± 6.9	7.3 ± 6.8	0.87
Erythrocyte Sedimentation Rate, 1 h	31.3 ± 23.3	29.3 ± 23.8	0.69
C-reactive protein, mg/dl	1.9 ± 2.3	2.4 ± 2.5	0.38
Patient pain, VAS 0-100	44.5 ± 17.8	43.8 ± 20.5	0.87
Patient Global Assessment, VAS 0-100	46.2 ± 18.1	44.8 ± 22.1	0.76
Evaluator Global Assessment, VAS 0-100	44.1 ± 18.5	40.1 ± 20.3	0.34

*Mean ± standard deviation, or % of patients, as appropriate.

Table II. Response to one week intermediate dose glucocorticoids in patients with and without preceding low-dose glucocorticoids*.

	No glucocorticoids (n = 48)	Low-dose glucocorticoids (n = 41)	*p*-value
Disease Activity Score 28 (DAS28)	1.4 ± 1.1	1.1 ± 1.0	0.14
Simplified Disease Activity Index (SDAI)	11.1 ± 13.4	11.1 ± 11.4	0.99
Clinical Disease Activity Index (CDAI)	9.9 ± 12.8	8.9 ± 9.5	0.69
Swollen joint count, 0-28	3.4 ± 4.4	3.6 ± 3.5	
Tender joint count, 0-28	3.5 ± 6.7	2.2 ± 5.6	
Erythrocyte Sedimentation Rate, 1 h	16.4 ± 16.0	10.8 ± 15.2	0.26**
C-reactive protein, mg/dl	1.1 ± 1.9	1.4 ± 2.5	
Patient pain, VAS 0-100	21.3 ± 19.9	16.6 ± 19.9	
Patient Global Assessment, VAS 0-100	19.8 ± 23.0	18.2 ± 23.6	
Evaluator Global Assessment, VAS 0-100	19.7 ± 16.5	15.1 ± 18.4	
Health Assessment Questionnaire, 0-3	0.3 ± 0.5	0.2 ± 0.3	

*Mean ± standard deviations of improvement from baseline to endpoint.
**Wilk's Lambda statistics, multivariate analysis.

ures between the two study populations ($p = 0.26$, Wilk's Lambda statistics).
Finally, we asked if baseline or preceding characteristics of GC therapy could have influenced the outcome. In these analyses, neither baseline GC doses nor cumulative doses of preceding low-dose GC therapy or duration of therapy were found to correlate with responsiveness to the high dose GC treatment (Table III).

Discussion

In this study, short-term application of 250mg prednisolone over one week had a significant beneficial effect on all clinical, serological and functional measures in RA. This effect was seen to the same extent whether patients had been pre-treated with low-dose GC or not. Although in current clinical practice steroid boosts are employed regardless of pre-existing low-dose GC treatment, it has not been investigated hitherto if subsequent effectiveness of GC boosts may be impaired in patients already experiencing the effects of low-dose GC therapy. The findings in this study on systematically tested patients with active RA reveal that low doses of GC do not reduce the responsiveness of disease activity measures to higher GC doses and, thus, suggest that steroid resistance is not induced by low-dose GC to a clinically relevant degree in RA.
It has been shown that low-dose GC can lead to a dose dependent and nearly complete down-regulation of the glucocorticoid receptor (18, 19). Reduction of GC receptors has been suggested to constitute one important factor in conveying GC resistance (28), although this issue is still under debate (29, 30). In the present study we show that, at least clinically, a resistance to higher GC doses is not seen in patients receiving long-term treatment with low doses of GC. Although we did not assess changes in glucocorticoid receptor density, nor performed binding studies and, therefore, do not completely resolve the issue of steroid resistance on the molecular level, we aimed to address this question from the perspective of clinicians. We also did not assess changes in serum cortisol level and focused our analysis on the question if a clinically important decrease in therapeutic effectiveness of higher dose GC has to be expected in patients currently receiving low-dose GC therapy. In fact, this was not the case, even though in the low-dose GC group baseline steroid treatment was not continued, and, therefore, the incremental steroid dose in that group was smaller than in the group without GC treatment.
Our finding pertains to all aspects of disease activity measurements, from joint counts to acute phase responses, and thus to more subjective as well as objective disease activity measures. Although the group sizes of our study may not allow detecting statistical significance on small differences in effectiveness between the two groups and we cannot exclude the existence of a small number of individuals in whom GC resistance might, in fact, have been induced, this would not be expected to have an impact on the clinical practice of GC application. Also, we did not correct for multiple analyses to prevent from false negative results.
Although GC are sometimes regarded disease-modifying drugs and have been shown to prevent radiographic progression of RA, the aim of this study was not to look at long-term outcomes and changes in radiographic scores, but rather to assess the effects of a steroid boost therapy on short-term responsiveness of disease activity, the improvement of which usually is the indication for success of this therapeutic approach. We were, therefore, interested in the immediate impact of a steroid boost on

Table III. Correlation of daily dose, duration, and cumulative dose of long-term low-dose glucocorticoid therapy with the degrees of response to intermediate dose flare therapy with steroids.

Characteristics of low-dose therapy at baseline	Median (quartiles)	Correlation with improvement in various disease activity indices (Spearman's rho and associated *p*-value)		
		DAS28 improvement	SDAI improvement	CDAI improvement
Presenting dose (mg/day)	6.5 (4.8; 6.2)	$r = 0.18$ ($p = 0.27$)	$r = 0.4$ ($p = 0.39$)	$r = 0.08$ ($p = 0.64$)
Duration of therapy (months)	32.7 (5.2; 26.6)	$r = 0.17$ ($p = 0.28$)	$r = 0.17$ ($p = 0.31$)	$r = 0.03$ ($p = 0.85$)
Cumulative dose (g)	6.4 (0.8; 5.1)	$r = 0.22$ ($p = 0.18$)	$r = 0.23$ ($p = 0.17$)	$r = 0.08$ ($p = 0.63$)

DAS28: Disease Activity Score based on 28 joint count evaluation; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index.

clinical and serological markers of disease activity in patients who are in need of fast relief of their disease symptoms. Likewise, the use of prednisone at 25 –50mg/day for prolonged periods is not considered a therapeutic option, given the adverse toxicity profile of high dose steroids in the longer term. The longer term application and effects of this regimen were therefore not subject of the present study. In addition, steroid doses used for the purpose of flare therapy in clinical practice are highly variable, and the regimen used in this study may be higher than in many rheumatologist´s clinical practice. However, it is unlikely that a difference between the two groups would be seen if lower steroid doses were used, since the overall level of response for both groups would be smaller.

Importantly, although this was an open-label trial, the assessor was fully blinded to patient characteristics. Patients with and without low-dose GC had the same inclusion criteria and similar disease activity at baseline and entered the trial in a random, parallel fashion. In this way, potential biases in assessment and differential stratification of the two patient groups by level of disease activity at baseline were unlikely.

In conclusion, our study reveals that higher doses of GC can exhibit a considerable clinical effect on RA disease activity, irrespective of the presence, duration or dose of preceding low-dose therapy with glucocorticoids. Thus, long-term low-dose GC therapy does not confer clinical resistance to higher dose flare therapy with glucocorticoids, providing the evidence for the common practice to employ steroid boosts in RA regardless of the presence or absence of concurrent low-dose therapy.

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