The clinical effect of glucocorticoids on wellbeing in patients with RA may be masked by decreased use of additional therapies.
Abstract

Objective
In our former analysis in patients with early active rheumatoid arthritis (RA), treated with 10 mg prednisone or placebo discrepancies between both groups were found. In contrast to a significant retardation of joint damage in the prednisone group compared to the placebo group, there were no differences in clinical variables between the 2 groups, attributable to more use of additional therapy in the placebo group than in the placebo group.

Aim of the study: to investigate whether this discrepancy, regarding different dimensions of RA, would extend to variables of wellbeing.

Methods
A double blind, randomized, placebo-controlled clinical trial, duration 2 years (10 mg prednisone or placebo), including an open follow-up third year of 81 patients with early (≤ 1 year) active previously untreated RA. Forty-one patients were allocated to 10 mg prednisone orally daily and 40 to placebo. Analgesics, NSAIDs, restricted use of local steroid injections and use of physiotherapy were allowed in both groups. After 6 months sulphasalazine (2 gr daily) could be prescribed as “rescue” therapy in both groups. At start and every 6 months thereafter 2 health status questionnaires VDF (Dutch version of the HAQ) and IRGL (Dutch version of the AIMS) were administered and every 3 months a visual analogue scale (VAS) for morning pain. Furthermore, disease activity and radiological scores were assessed.

Results
Scores of the VDF showed no statistically significant differences between the prednisone group and the placebo group. No statistical differences were found in almost all parameters of the IRGL between groups. At 3 months the VAS morning pain and the VAS general wellbeing showed improvement in the prednisone group comparable with the transient improvement in some other disease activity variables. In the prednisone group the cumulative use of NSAIDs, analgesics, local steroid injections and sessions of physiotherapy was about 50% of that of the placebo group.
Conclusion
Although significant retardation of joint damage in the prednisone group indicates better disease control, no differences between both groups were found for variables of wellbeing. This discrepancy can probably be attributed to increased use of additional therapy in the placebo group. So, the use of additional therapies should thus be taken into account in analyzing and interpreting results of clinical drug trials.
INTRODUCTION

In daily clinical practice with patients with rheumatoid arthritis (RA), most physicians assume a direct association between disease activity, general wellbeing and joint damage late in the course of the disease. Therapeutic approaches of patients with RA are based on these assumptions. Frequently, in the treatment of these patients, in addition to disease modifying antirheumatic drugs (DMARDs), glucocorticosteroids (GC) are used for instantaneous relieve of symptoms and for improvement of general wellbeing. Recently, several studies on RA suggest also disease-modifying properties of long-term low-dose GC. These studies describe effects on disease activity and joint damage whereas few studies describe the effects on wellbeing. In most of these studies the use of additional therapies such as analgesics, NSAIDs, local injections and physiotherapy are not taken into account. In healthy adult volunteers and non-RA patients the effects of GC on cognitive functioning and psychological side effects have extensively been described and reviewed. In our analysis of patients with early active previously untreated RA, we saw no enduring differences in variables of disease activity and physical functioning between the prednisone 10 mg group and the placebo group. In the prednisone group however, better disease control was achieved, as significant retardation of joint damage occurred, compared the placebo group. This discrepancy between radiological and clinical effects could be attributed to the greater amount of analgesics and NSAIDs used in the latter group. It thus makes a difference whether suppression of signs and symptoms is achieved with low dose prednisone or extra analgesics and NSAIDs. This difference might extend to variables of wellbeing. From daily practice, low-dose prednisone could be hypothesized to have more effects on wellbeing than extra analgesics and NSAIDs.

There are more data suggesting that disease activity and wellbeing are not always well balanced or strictly coupled in the course of RA. Androgens as adjuvant treatment led to improvement in general wellbeing of postmenopausal women with active RA but not in disease activity. In a study comparing the use of alternative or complementary therapy (CM) with conventional therapy of patients with RA, a higher impact of RA in the absence of worse disease was perceived by users of CM in several domains of life, especially psychological functioning.

The aim of the present study is to investigate whether the discrepancy found in our analysis between disease activity variables and joint damage also extends to variables of wellbeing and to investigate the role of additional therapies in interpreting results of clinical drug trials.
PATIENTS AND METHODS

Patients

From October 1992 through October 1995, eighty-one out of 118 eligible consecutive outpatients, who were at least 18 years of age, with early previously untreated RA (disease duration less than one year), according the 1986 ARA-classification, were enclosed in the study. The patients were recruited from the Departments of Rheumatology of the Deventer and Zutphen Hospitals, the Netherlands, and randomly allocated in blocs of 10 subjects to one of two groups of treatment for two years: 1) two tablets of 5 mg prednisone once daily at breakfast (=10 mg), 2) placebo in the same way. Use of NSAIDs, physical therapy and paracetamol was free of choice. Restricted use of local GC injections was allowed. After 6 months sulphasalazine (2 gr. daily) could be prescribed as additive “rescue” medication. The decision to add sulphasalazine was based on clinical grounds (activity of RA).

Variables

At start and every 6 months thereafter, two validated health status questionnaires were administered:

1) VDF: functional disability assessed with a validated Dutch version of the Health Assessment Questionnaire. The VDF contains of 20 items, which are grouped into 8 scales representing dressing, arising, eating, walking, hygiene, reach, grip and outside activity. Patients are asked about the ability to perform activities without help, with responses ‘able to do without difficulty’ (score 0), ‘able to do with some difficulty’ (score 1), ‘able to do with much difficulty’ (score 2) and ‘unable to do’ (score 3). Furthermore, patients are asked whether or not they use a cane, a wheelchair, an adapted bed or chair, or devices for dressing, hygiene, or eating and whether or not they are assisted in performing any of the activities of the 8 scales. The total VDF score may vary from 0-3, 0 representing the best (no problems) and 3 the worst score.  

2) IRGL: Impact of Rheumatic diseases on General health and Lifestyle. The IRGL is a health status questionnaire, developed from the Arthritis Impact Measurement Scales 1 (AIMS 1) assessing physical, psychological and social functioning as well as the impact of the disease on daily life. The scales of the IRGL differ in their individual ranges and are expressed in the original direction: for example, high values on the scale pain and low values on the scale mobility and self care indicate a poor health status. The IRGL has been validated in the Netherlands.
The IRGL assesses the various domains of health as follows:

- Physical wellbeing: 21 items: 7 for the scale mobility, 8 for the scale self care and 6 for the scale pain
- Psychological wellbeing: 22 items: 6 for the scale depressive mood, 6 for the scale cheerful mood and 10 for the scale anxiety
- Social wellbeing: 13 items: 2 for quantitative aspects of the scale of social support and 11 for qualitative aspects forming 3 scales: potential exchange of emotional support, actual exchange of emotional support and mutual visits
- Arthritis Impact: 12 items of the impact of RA on daily life: work, housekeeping, hobbies, holidays, leisure, sexuality, eating and sleeping habits, relationships with the partner, family and friends and family life

We also assessed every 3 months a visual analogue scale (VAS) for early morning pain and one for general wellbeing regarding the past week, both scales ranging from 0 to 100 mm, 0 representing the best and 100 the worst score.

From start and every 3 months thereafter the number of NSAIDs, analgesics, physical therapy and local intraarticular injections was assessed.

As parameters for disease activity were assessed C- reactive protein (CRP), early morning stiffness recorded in minutes, the 28 joint score for tenderness and the 28 joint score for swelling and grip strength. At start and every 6 months thereafter, radiographs of hand and feet were performed and scored according to the Sharp/van der Heijde method.1, 14- 16

**Statistical analysis**

All statistical analyses to evaluate the effect of treatment were performed according to the ‘intention to treat ‘principle. For the 10 patients who dropped out during the study, outcomes of the last measurements were carried forward, with the exception of the radiological scores. For radiological scores, missing data were estimated using individual progression as indicated by available scores; last measurements carried forward would have been too positive as estimation, suggesting no further deterioration. For the VDF, IRGL, the VAS morning pain, the VAS general wellbeing, CRP, early morning stiffness, the 28 joint score for swelling and the 28 joint score for pain, mean differences in changes from baseline between the two groups were tested at 24 months with two-sided T-tests or the Mann-Whitney U-test, where appropriate (see Table 1).

Baseline variables and patients’ characteristics were tested for statistically significant differences between the two groups using unpaired, two-sided T-tests or Mann-Whitney U tests, where appropriate, for means and with Fishers’ exact
EFFECT OF GLUCOCORTICOIDS ON WELLBEING

Table 1

Baseline characteristics of the 81 patients with early RA γ (numbers, means and standard deviations)

<table>
<thead>
<tr>
<th></th>
<th>Prednisone n = 40</th>
<th>Placebo n = 41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>60 (14)</td>
<td>64 (12)</td>
</tr>
<tr>
<td>Male/female (n)</td>
<td>17 / 23</td>
<td>12 / 29</td>
</tr>
<tr>
<td>IgM rheumatoid factor positive ‡ (n patients)</td>
<td>29</td>
<td>31</td>
</tr>
<tr>
<td>Patients with erosive disease (n) #</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Variables of wellbeing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Disability score (VDF)*</td>
<td>0.8 (0.6)</td>
<td>1.0 (0.7)</td>
</tr>
<tr>
<td>- IRGL mobility*</td>
<td>21.6 (6)</td>
<td>19.2 (6)</td>
</tr>
<tr>
<td>- IRGL self care*</td>
<td>25.6 (5)</td>
<td>25.6 (5)</td>
</tr>
<tr>
<td>- IRGL pain*</td>
<td>14.9 (4)</td>
<td>16.7 (4)</td>
</tr>
<tr>
<td>- VAS morning pain³</td>
<td>28 (20)</td>
<td>34 (25)</td>
</tr>
<tr>
<td>- VAS general wellbeing ¶</td>
<td>31 (23)</td>
<td>41 (23)</td>
</tr>
</tbody>
</table>

γ no statistically significant differences between the two groups
‡ RF status was considered positive when the IgM-RF was 25 IU/ml or more, a cut-off point resulting in a false-positive test for less than 5% of the general population.
* VDF (Vragenlijst Dagelijks Functioneren) is a Dutch version of the HAQ questionnaire, its score ranging from 0-3, 0 representing the best (no problems) and 3 the worst score 11.
# Sharp-van der Heijde erosion score of ≥ 4 was considered to be erosive and 0-3 non-erosive 6.
° IRGL Impact of Rheumatic diseases on General health and Lifestyle; mobility, range 7-28, 7 representing the worst score and 28 the best score; self care, range 8-32, 7 representing the worst score and 28 the best score; pain, range 6-25, 6 representing the worst score and 25 the best score 12.
³ Visual analogue scale (VAS) of morning pain 0-100 mm., 0 the best score, 100 the worst score
¶ Visual analogue scale (VAS) of general wellbeing 0-100mm, 0 the best score, 100 the worst score

Individual patient improvement was assessed according to the modified 20% ACR improvement criteria: details are described in our earlier report.¹

All analyses were performed with the statistical package “Number Cruncher Statistical System” version 97 (Jerry Hintze, Kaysville, Utah).

RESULTS

Patient characteristics, VDF, VAS early morning pain, VAS general wellbeing and 3 domains of the IRGL at the start of the study are shown in Table 1: there were no statistically significant differences between the two groups. All patients were Caucasian except for two in the prednisone group.
Ten patients discontinued the study: 4 in the prednisone group and 6 in the placebo group.¹ No patient discontinued the two-year study for reasons of adverse events of the study medication in either group. After 6 months 39 out of the 71 patients who completed this study received suphasalazine as additional antirheumatic therapy on clinical grounds: 20 in the placebo and 19 in the prednisone group.

The use of analgesics and NSAIDs in the prednisone group was about 50% of that of the placebo group as was also the case for the number of local steroid injections and sessions of physiotherapy.¹

**Wellbeing variables (Table 2; Figure 1-5)**

Scores of the VDF showed no statistically significant differences (see Figure 1). In the items of the scales of the IRGL at 6, 12 and 24 months statistically significant differences between the groups were seen for depressed mood and potential support in favor of the prednisone group; no differences were seen in the other items of the scales (see Table 2; Figure 2,3). There were statistically significant differences at 3 months in the VAS early morning pain and the VAS general wellbeing between the prednisone group and the placebo group in favor of the prednisone group (see Figure 4,5).
Table 2

Effect of treatment on IRGL scales of patients with early RA; the prednisone group (pred) versus the placebo group (plac) (means, sem, p-value)

<table>
<thead>
<tr>
<th>Scale</th>
<th>Range</th>
<th>Pred</th>
<th>SEM</th>
<th>Plac</th>
<th>SEM</th>
<th>p</th>
<th>Pred</th>
<th>SEM</th>
<th>Plac</th>
<th>SEM</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobility</td>
<td>8-32</td>
<td>21.6</td>
<td>0.6</td>
<td>21.4</td>
<td>0.6</td>
<td>0.09</td>
<td>20.9</td>
<td>0.6</td>
<td>21.5</td>
<td>0.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Self care</td>
<td>8-32</td>
<td>25.6</td>
<td>0.5</td>
<td>25.6</td>
<td>0.5</td>
<td>1.0</td>
<td>28.2</td>
<td>0.7</td>
<td>27.0</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Pain</td>
<td>6-25</td>
<td>14.9</td>
<td>0.4</td>
<td>16.7</td>
<td>0.4</td>
<td>0.09</td>
<td>12.1</td>
<td>0.6</td>
<td>13.5</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>0-24</td>
<td>3.2</td>
<td>0.5</td>
<td>4.7</td>
<td>0.4</td>
<td>0.02**</td>
<td>3.3</td>
<td>0.4</td>
<td>3.1</td>
<td>0.4</td>
<td>0.06</td>
</tr>
<tr>
<td>Cheerful mood</td>
<td>okt-24</td>
<td>10.9</td>
<td>0.5</td>
<td>10.3</td>
<td>0.6</td>
<td>0.5</td>
<td>11.0</td>
<td>0.5</td>
<td>11.6</td>
<td>0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5-20</td>
<td>19.0</td>
<td>0.5</td>
<td>19.6</td>
<td>0.6</td>
<td>0.7</td>
<td>17.9</td>
<td>0.6</td>
<td>17.6</td>
<td>0.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Potential support</td>
<td>5-20</td>
<td>14.7</td>
<td>0.4</td>
<td>14.9</td>
<td>0.4</td>
<td>0.9</td>
<td>16.0</td>
<td>0.4</td>
<td>15.5</td>
<td>0.4</td>
<td>0.004**</td>
</tr>
<tr>
<td>Actual support</td>
<td>00-xx</td>
<td>6.7</td>
<td>0.2</td>
<td>6.6</td>
<td>0.2</td>
<td>0.8</td>
<td>6.5</td>
<td>0.2</td>
<td>6.8</td>
<td>0.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Number of friends</td>
<td>2-8</td>
<td>7.1</td>
<td>0.5</td>
<td>12.4</td>
<td>0.6</td>
<td>0.01**</td>
<td>5.0</td>
<td>0.4</td>
<td>8.1</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Exchange of visitors</td>
<td>1-4</td>
<td>6.0</td>
<td>0.2</td>
<td>6.0</td>
<td>0.1</td>
<td>0.2</td>
<td>3.0</td>
<td>0.2</td>
<td>3.4</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Impact on activities</td>
<td>1-4</td>
<td>9.6</td>
<td>0.4</td>
<td>11.4</td>
<td>0.4</td>
<td>0.1</td>
<td>8.5</td>
<td>0.4</td>
<td>9.0</td>
<td>0.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Impact on sexuality</td>
<td>1-4</td>
<td>1.6</td>
<td>0.1</td>
<td>1.6</td>
<td>0.1</td>
<td>0.9</td>
<td>3.8</td>
<td>0.2</td>
<td>3.0</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Impact on eating and sleeping</td>
<td>2-8</td>
<td>2.9</td>
<td>0.2</td>
<td>3.4</td>
<td>0.2</td>
<td>0.2</td>
<td>2.9</td>
<td>0.2</td>
<td>3.4</td>
<td>0.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Impact on nutrition/sleep</td>
<td>2-8</td>
<td>2.8</td>
<td>0.2</td>
<td>3.1</td>
<td>0.1</td>
<td>0.4</td>
<td>2.6</td>
<td>0.2</td>
<td>2.7</td>
<td>0.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Impact on ADL</td>
<td>1-4</td>
<td>16.8</td>
<td>0.6</td>
<td>19.0</td>
<td>0.6</td>
<td>0.1</td>
<td>15.4</td>
<td>0.6</td>
<td>16.8</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Impact on relationship partner</td>
<td>1-4</td>
<td>11.7</td>
<td>0.1</td>
<td>15.0</td>
<td>0.1</td>
<td>0.5</td>
<td>1.8</td>
<td>0.8</td>
<td>2.0</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Impact on family life</td>
<td>1-4</td>
<td>1.5</td>
<td>0.1</td>
<td>1.5</td>
<td>0.1</td>
<td>1.0</td>
<td>6.7</td>
<td>0.5</td>
<td>2.1</td>
<td>0.1</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*p<0.05 between groups. At 6 months also statistically significant differences between both groups for potential support p=0.03 and at 18 months for depressed mood p= 0.03; data not shown.

**p<0.05

Disease activity variables

In our study, patients of the prednisone group showed improvement in 8 clinical parameters in the first 3 months compared to the placebo group. The clinical improvement in the prednisone group was transient: after 6 months the only clinical variables showing statistically significant differences were the 28 joint score for tenderness and the grip strength. Most of the clinical variables exhibited no statistically significant differences from baseline between the two groups although the actual improvement was slightly in favor of the prednisone group, reaching statistical significance for the 28 joint score for tenderness (p=0.01). Grip strength improved significantly and consistently in the prednisone group. Thirty-three percent of
Figure 2. The IRGL scale, potential support of patients with early RA treated with prednisone compared to placebo (means, SEM).

\( p = 0.05 \) at 6 months, 0.04 at 12 and 0.004 at 24 month

IRGL Impact of Rheumatic diseases on General health and Lifestyle; mobility, range 7-28, 7 representing the worst score and 28 the best score; self care, range 8-32, 7 representing the worst score and 28 the best score; pain, range 6-25, 6 representing the worst score and 25 the best score.\(^\text{12}\)

Figure 3. The IRGL scale, depressed mood of patients with early RA treated with prednisone compared to placebo (means, SEM).

\( p = 0.02 \) at start and 0.03 at 18 months

IRGL Impact of Rheumatic diseases on General health and Lifestyle; mobility, range 7-28, 7 representing the worst score and 28 the best score; self care, range 8-32, 7 representing the worst score and 28 the best score; pain, range 6-25, 6 representing the worst score and 25 the best score.\(^\text{12}\)
Figure 4. VAS (visual analogue scale) morning pain of patients with early RA treated with prednisone compared to placebo (means, SEM).  
$p = 0.0003$ at 3 months  
Visual analogue scale (VAS) of morning pain 0-100 mm., 0 the best score, 100 the worst score.

Figure 5. VAS (visual analogue scale) general wellbeing of patients with early RA treated with prednisone compared to placebo (means, SEM).  
$p = 0.003$ at 3 and $0.04$ at 6 months  
Visual analogue scale (VAS) of general wellbeing 0-100 mm., 0 the best score, 100 the worst score.
patients in the prednisone group satisfied the modified 20% ACR individual patient improvement criteria and 24% of patients did in the placebo group at 12 months and 30% and 22%, respectively, at 24 months.

**Joint damage**

At the start of the study there was no statistically significant difference in joint damage in the prednisone group compared to the placebo group. After one and two years there were statistically significant differences between both groups in favor of the prednisone group, increasing in time.

**DISCUSSION**

In our study with long term low-dose GC treatment in patients with early active previously untreated RA compared to placebo we found a transient amelioration of disease activity but a significant ongoing reduction in joint damage.\(^1\)

The aim of this study was to investigate general wellbeing in these patients and the role of additional therapies in evaluating the effects of the different treatment strategies. In daily practice GC lead to immediate relief of clinical symptoms and improvement of general wellbeing in patients with RA but relatively little is known about the long term effects on parameters of wellbeing.\(^17\) In the long term, functional disability of patients with RA will be affected not only by current inflammatory activity but also by structural joint damage.\(^18\) In a study comparing disease activity, joint destruction and functional capacity over the course of RA, functional capacity appears to be associated with disease activity in early RA and with joint damage in late disease.\(^19\) In a reappraisal of HAQ-disability in RA as a function of disease over time, the HAQ may be an inadequate model due to the patient’s upward reappraisal of functional ability with increasing time.\(^20\)

Over time, we found no enduring differences between the groups for most variables. Scores of the VDF (Dutch version of the HAQ) showed some improvement in the prednisone group, but no statistically significant differences (Figure 1). In the domains of the IRGL, 3 items were statistically significantly different in favor of the prednisone group at some points of time (Figure 2,3). There was a transient improvement in the VAS early morning pain as well as in the VAS general wellbeing (Figure 4,5).

Little is known about the use and effects of additional therapies such as analgesics, NSAIDs, local injections and physiotherapy on aspects of general wellbeing in studies of different therapy strategies in patients with RA. In the present
study the cumulative use of these additional therapies in the prednisone group was 50% of that in the placebo group. In another study of patients with RA on the effectiveness of early treatment with DMARDs also a doubling of intra-articular injections was found in the first year in the non-DMARD versus the DMARD group (44% vs. 22%). In spite of better disease control, reflected by significant inhibition of joint damage in the prednisone group vs. the placebo group, no difference in wellbeing variables was found, probably due to higher use of additional therapy in the placebo group. The same result was found for clinical disease activity variables.

Therefore, in future clinical drug trials, the use of additional therapies should thus be taken into account analyzing clinical differences in effect; clinical and wellbeing variables not always accurately reflect disease control.

REFERENCES


