Glucocorticoids in rheumatoid arthritis: lessons from the Utrecht study

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ABSTRACT

The lessons from the Utrecht study on glucocorticoid therapy in early rheumatoid arthritis and of the spin-off and follow-up studies are reviewed. The data indicate that: glucocorticoids are DMARDs, the joint-sparing effect is predominantly on erosions, glucocorticoids do not influence the percentage of patients developing erosive disease, and the gain in joint-sparing effect persists after the stop of treatment. Further lessons are that the size of the joint-sparing effect and the (presumed) size of the symptomatic effect of glucocorticoids depend on co-therapies. Additional DMARDs must be added to glucocorticoids for maximum effect on radiographic progression. Finally, low-dose glucocorticoids are safer than often thought.

Introduction

Rheumatology has come a long way in the therapy of rheumatoid arthritis (RA) since the publication in 1949 showing that cortisone dramatically ameliorated the symptoms of RA. At that time, the therapeutic strategy of RA was characterised by the pyramid approach (Fig. 1). This implied that all patients got basic therapy consisting of life style advice, physiotherapy, analgesic agents and non-steroidal anti-inflammatory drugs. Only those with persisting considerable signs and symptoms were given a disease-modifying anti-rheumatic drug (DMARD). The reluctance to use DMARDs early in the disease course was based on the severe potential adverse events of the available DMARDs at that time, especially gold salts and d-penicillamine. The introduction of methotrexate provided the rheumatologist with a DMARD with greater efficacy, safety and possibilities of combination therapy with other DMARDS and titration of the dose to the disease activity of the individual patient. The aim of drug treatment – including glucocorticoids – which initially was clinically relevant improvement regarding disease activity, signs and symptoms gradually shifted to the lowest disease activity attainable and inhibition of progression of radiological joint damage. Although early data shortly after their introduction had suggested potential slowing of radiographic progression (1), glucocorticoids for decades after their introduction had been prescribed primarily for their symptomatic effects. The changed aims of therapy warranted investigation into their potential slowing of radiographic progression. This is the background of the Utrecht study.

The Utrecht study

In 1992, we started a double-blind randomised placebo-controlled clinical trial of 2 years' duration looking at the effect of medium-dose glucocorticoids as initial disease-modifying monotherapy in DMARD-naïve patients with early (disease duration <1 year) active RA (2). Eighty-one of those patients, who had not been treated with a DMARD before were randomised to 10 mg prednisone orally daily or placebo-prednisone. After six months, sulphasalazine (2 gr daily) could be added to the therapy if needed. The study had been approved by the ethics committee. Nowadays, it would be considered unethical to compare the effects of prednisone *versus* those of placebo in patients who do not receive a DMARD for at least 6 months. Radiographs of hands and feet were taken at entry and every 6 months and scored with the Sharp-vanderHeijde score (3). The most important result of the study was that from month 12 on, radiological scores showed less progression of joint damage in the prednisone-treated group compared to the placebo group, which was a statistically significant and clinically relevant finding. Nevertheless, progression of joint damage still was

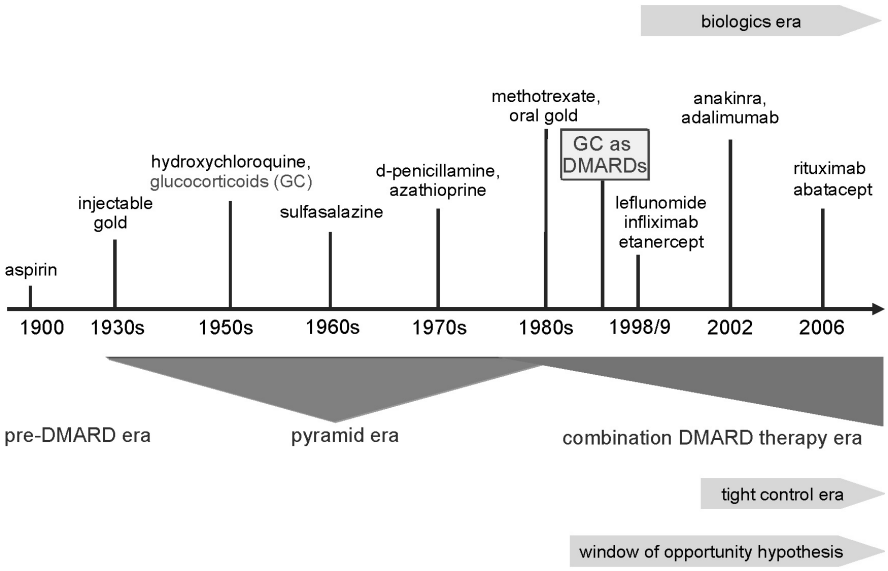

Fig. 1. Development in time of therapies, therapeutic strategies and paradigms for rheumatoid arthritis. X-axis: time scale, not linear. Several DMARDs were generally clinically applied in rheumatoid arthritis only years after their introduction to the market; the primary indication of most of the conventional DMARDs was not rheumatoid arthritis, *e.g.* for hydroxychloroquine it was malaria.

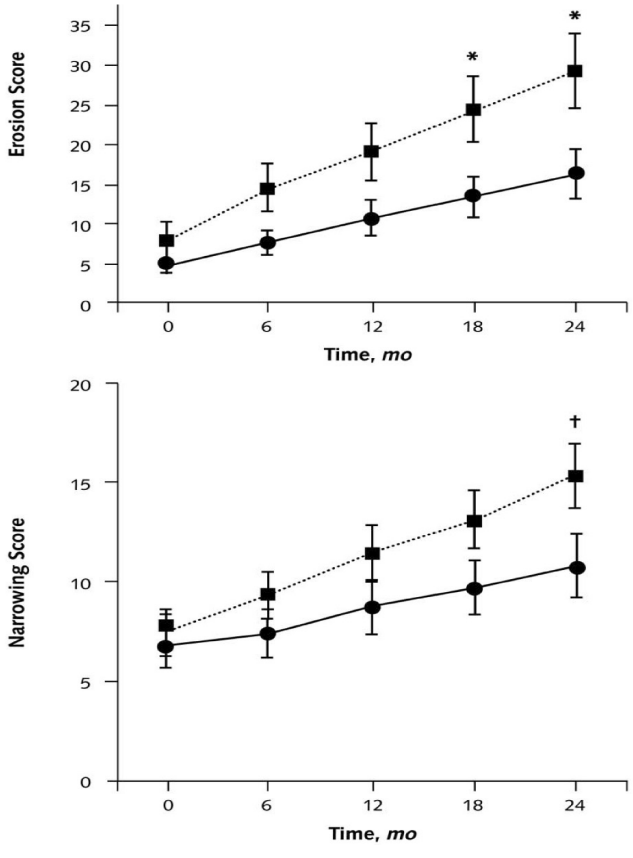

Fig. 2. Radiographs of hands and feet scored with the Sharp-vander-Heijde score, separately for joint erosions and joint narrowing during the 2 year Utrecht study. X-axis: time scale, months; Y-axis: radiographic score according to Sharp-vanderHeijde, note: different scaling of Y-axes for joint erosions and for joint narrowing; solid lines indicate the prednisone group; dotted lines indicate the placebo group; means and standard errors; * = p=0.05; † = p=0.02, comparing both groups.

considerable in the prednisone-treated group too. Our conclusion was that the use of glucocorticoids in this early stage of RA significantly retards the progression of radiological damage in hands and feet as seen on radiographs.

Lessons from the Utrecht study

There are several conclusions to draw from our study and related other studies by our own group and by other research groups. We will discuss those conclusions here in short.

Glucocorticoids are DMARDs

Our findings and similar research results from other research groups proved that glucocorticoids have disease-modifying properties (4), because they not only suppress signs and symptoms of RA, but also slow down the progression of radiological joint damage. Important is to note that this DMARD-effect has only be proven for therapy given during the first two years of RA - which is not to say this effects will be absent when treating patients with glucocorticoids in a later phase of their disease: this has not yet been investigated.

The joint-sparing effect of glucocorticoids is predominantly on erosions

The difference in total Sharp-vander-Heijde score between the two groups in our study was mainly based on difference in progression of erosive joint damage and less on difference in decrease in joint space width (Fig. 2). In several other studies inhibition of decrease in joint space width was even not found (5). Osteoclasts are directly activated by receptor activator of nuclear factor κβ ligand (RANKL) on activated T-cells (6); down regulation of RANKL within the joint by GC could be an important mechanism of inhibition of formation of joint erosions. In line with this hypothesis is the finding that in RANKL-knock out mice, experimental arthritis does not cause joint erosions (7), and that denosumab potentially inhibits formation of erosions in RA (8).

Glucocorticoids alone do not influence the percentage of patients with erosive disease

Although glucocorticoids have been proven to inhibit erosive progression in joints, we found in our trial described above and in the follow-up study from this trial (see below) that the percentage of RA-patients with erosive disease was similar in the (former) prednisone group, when compared to that in the (former) placebo group (Fig. 3) (2, 9). This finding is in line with the result that although glucocorticoids inhibit erosive progression, they do not stop it – see below.

The joint-sparing effect of glucocorticoids is only partial

Although our findings and those of other research groups were that the use of glucocorticoids in an early stage of RA significantly retards the progression of radiological damage in hands and feet, in all studies control of radiographic damage was only partial. This suggests that additional DMARD therapies are needed for better control of radiological joint damage.

The size of the joint-sparing effect of glucocorticoids depends on the co-medication

When comparing the joint-sparing effect of glucocorticoids in different studies, the effect of glucocorticoids in our study relative to placebo appeared greater compared to that in other studies, in which the effect glucocorticoids concomitantly with other DMARDs was compared with the effect of these DMARDs without glucocorticoid (10). It theoretically makes sense that the joint sparing effect size of glucocorticoids in patients concomitantly treated with anti-tumour necrosis factor drugs -which have great joint sparing properties- will be less compared to that in patients without these biologicals. Concomitant denosumab therapy in RA-patients possibly also could reduce the effect size of glucocorticoids on erosive joint damage, as denosumab is a monoclonal antibody for RANKL and this inhibition of RANKL inhibits activation of osteoclasts (11); whereas glucocorticoids via down regulation of RANKL have the same effect.

The (presumed) size of the symptomatic effect of glucocorticoids depends on co-therapies

Although a significant retardation of joint damage was observed in the prednisone group compared with the placebo-prednisone group in the Utrecht study, no differences in clinical variables between the 2 groups were observed, nor differences in physical disability (score Health Assessment Questionnaire) or quality of life (scores on the IRGL, a Dutch version of the Arthritis Impact Measurement Scales). An analysis into this discrepancy yielded that the overall use of physiotherapy had been significantly lower in the prednisone group compared to that in the placebo-prednisone group, especially in the first 6 months of the study (12). The total number of intra-articular glucocorticoid injections given in the prednisone group during the study had been 40% lower than that in the placebo-prednisone group; the consumption of paracetamol (acetaminophen) tablets in the prednisone group had been 49% lower compared to that in the placebo-prednisone group; also the cumulative consumption of NSAIDs over 24 months had been considerably lower. Our conclusion was that the clinical effect of glucocorticoids in patients with RA may be masked by diminished need and use of additional therapies and that the use of additional therapies should be taken into account when analysing differences in symptomatic effect between drugs (12).

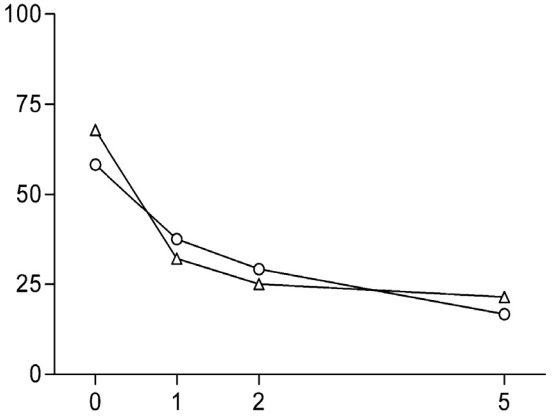

Fig. 3. Percentages of patients with non-erosive disease during Utrecht study and at follow-up.
Y-axis, percentages of patients, (formerly) randomised to prednisone therapy (open circles) and of patients, (formerly) randomised to placebo (open triangles). X-axis, time in years; five-year radiographic scores corrected for different follow-up periods. Non-erosive disease defined as an erosion score of the Sharp-vanderHeijde score of less than 4 units. No statistically significant difference between the two groups at any point in time

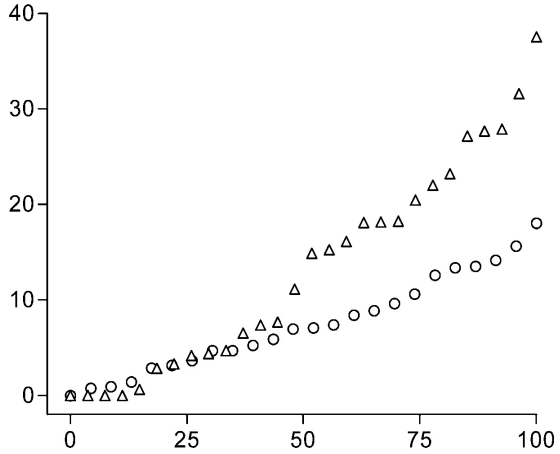

Fig. 4. Cumulative probability plots of mean yearly radiographic progression during 3 years of follow-up since the end of the 2-year Utrecht study.
Y-axis: radiographic score (total Sharp-vanderHeijde score); X-axis: cumulative probability. Each symbol represents a patient; circles indicate the scores of patients, formerly randomised to prednisone therapy and triangles those of patients, formerly randomised to placebo-prednisone.

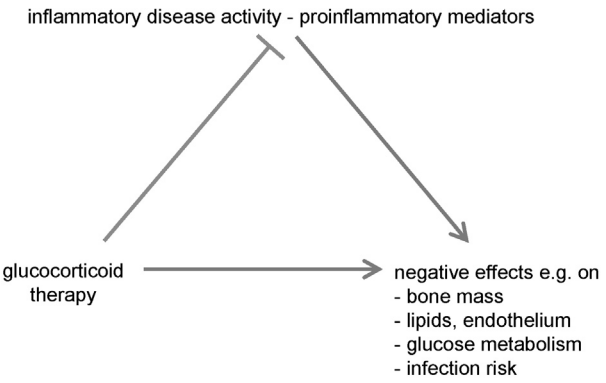

Fig. 5. Associations between glucocorticoid therapy, the inflammatory disease and specific negative effects.
Glucocorticoids inhibit the inflammatory process which could cause undesired effects, but these effects might also be adverse effects of high dosed glucocorticoids.
→ : mechanisms increasing the risk of negative effects
⊣ : mechanisms decreasing this risk.

The slowing down of radiographic joint damage during glucocorticoid treatment persists after discontinuation of this therapy

Radiographic scoring of hands and feet at about three years after the end of our 2-year Utrecht study in available patients was performed according to the Sharp-vanderHeijde method. Patients of the former prednisone group had significantly less progression compared to those of the former placebo group (Fig. 4) (9). Radiographic joint damage in the former prednisone group did not show an accelerated rate of progression during the follow-up period, compared to the rate during the study. We concluded that the slowing down of radiographic joint damage in patients with early active RA treated with prednisone, 10 mg/day for two years seems to persist after the end of prednisone treatment. This result is in line with the follow-up results of the COBRA-trial (13).

Low-dose glucocorticoids are safer than often thought

In our Utrecht study, adverse effects were mild (2). The risk of adverse effects of low-dose glucocorticoids often is overestimated. The first reason is the historical association of low-dose glucocorticoids with the adverse effect spectrum of high-dose glucocorticoids –there is a lack of literature data on the risk of low-dose glucocorticoids (14). The second reason is bias by indication. Patients with the more severe disease more frequently are prescribed glucocorticoids; in these patients the risk of negative effects and events is higher based on their higher disease activity and often more frequent comorbidities, compared to that of patients with lower disease severity, who do not need glucocorticoids. Third, some negative effects are more likely associated with the disease than with the glucocorticoid therapy (disease complications taken for glucocorticoid adverse effects) (15), and several negative effects are both associated with the disease treated and with glucocorticoids, but only in medium and high dosages. Examples are negative effects on bone mass, lipids, endothelium, glucose metabolism and infection risk (16-19). It could even be the case that glucocorticoid in lower dosages, by inhibiting the inflammatory process, might inhibit or balance these negative effects (Fig. 5). Studies into the real risk of adverse effects of low-dose chronic glucocorticoid therapy are needed.

Conclusion

Glucocorticoids are an effective anchor DMARD in therapeutic strategies with other DMARDs for the first two years of the disease. Research into the DMARD effects of glucocorticoids when prescribed after the first two years of RA is needed. The effect sizes of the inhibition of joint erosions and of the symptomatic effects of glucocorticoids depend on the co-therapy. Low-dose glucocorticoids are safer than often thought.

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