Glucocorticoid treatment in early rheumatoid arthritis

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ABSTRACT

Glucocorticoids (GCs) have been an invaluable tool in the treatment of patients with rheumatoid arthritis (RA) for decades, with a focus mainly on symptom management. In addition, several studies in the last 15 years have shown that GCs are also disease-modifying in patients with RA – which implies that they inhibit radiographic progression. These effects seem to be especially important in the early course of disease. Nonetheless, there is still a lack of knowledge concerning optimal therapeutic strategies with GCs, particularly regarding patient selection and optimal dosage schedules.

Introduction

The first steps to treat patients with rheumatoid arthritis (RA) with glucocorticoids (GCs) by P. Hench (1) evoked great enthusiasm, and he received the Nobel prize for that. However, the early experiences with the adverse events of GCs made experts recommend to reserve GCs for a temporary "bridge" therapy while waiting for the success of therapy with disease-modifying anti-rheumatic drugs (DMARDs), or for life-threatening extra-articular diseases and especially organ involvement. Over the years, GCs have been used for RA patients with varying enthusiasm and substantial regional and national differences, textbooks have even cautioned against their use. However, in daily practice the majority of patients with RA take GCs. Although inhibition of radiographic progression with GCs has already been documented in the 1950s (2), the main objective of therapy with GCs in the first 40 years of the treatment history has largely been symptom control aiming for rapid reduction of pain and inflammation. Indeed, the link between inflammation and structural damage has not always been as clear as nowadays.

In 1995, the first controlled clinical study on low-dose GC therapy did not only report a decrease in pain, disability and articular scores after only 3 months of treatment with 7.5 mg prednisolone/day compared to placebo, but also a reduction of radiographic progression after longer term treatment with GCs for 2 years (3). One year after GC discontinuation joint destruction resumed (4). These findings set the scene for more studies and discussions on disease-modifying effects of GCs by reducing the probability for an erosive course of RA and by reducing the progression in patients with established erosive RA. Today it is well established that the suppression of inflammation is of critical importance for the prevention of radiographic damage in RA.

The effect of glucocorticoids on signs, symptoms and function

Treatment with GCs is capable of producing a rapid and often clinically impressive relief of symptoms in patients with RA, most easily demonstrated over the first days, weeks and months of treatment. In the BARFOT (Better Anti-Rheumatic Farmacotherapy) study, the addition of 7.5 mg prednisolone/day to DMARDs induced a significant decline in DAS-28 and HAQ values after 3 months compared to placebo which slightly decreased over the following 21 months (5). Likewise in a tight control setting, patients on GCs (12.5 mg/day for 2 weeks, then tapered to 6.25 mg/day) achieved higher rates of clinical remission during the first and a higher probability of sustained remission during the second year (6).

The symptomatic effect of GCs is rather likely to be dose-dependent but this has not been formally studied to date. In another study on RA patients treated with only 5 mg prednisolone/day, the clinical effect of this dose was found to be limited, and the difference to placebo did not reach statistical significance (7). On the other hand, as strongly suggested by clinical experience 14 mg prednisone/day may be rather ef-

ficacious – as recently documented by Pincus *et al*. (8). In a Cochrane review (9), the authors concluded that low-dose GC therapy (not exceeding 15 mg prednisolone/day) is clinically highly effective and, of note, that short-term placebo-controlled trials studying the clinical effect of low-dose prednisolone or other corticosteroids are no longer necessary.

Nonetheless, the advantages of symptomatic use of GCs need to be balanced against the side-effects of this medication. In daily practice, the indication and the dosage for symptomatic use of GCs is usually based on the doctor's experience who has to take into account the patient´s fears and beliefs as well. The mid-term GC dosage will depend greatly on short-term treatment responses. Over time, the experienced rheumatologist will always try to find the lowest GC dosage possible by tapering the dose according to the clinical symptoms and complaints of the patients as well as biomarkers of inflammation such as C-reactive protein (CRP) (10).

The effect of glucocorticoids on radiological joint damage in general

There is evidence from several studies that GC treatment inhibits radiographically detected joint damage, this includes low GC dosages (Table I). Only one study failed to show a significant effect (11), but the reading method has been criticised (12). A Cochrane review (13) concluded that "even in the most conservative estimate, the evidence that GCs given in addition to standard therapy can substantially reduce the rate of erosion progression in RA is convincing."

A meta-analysis on radiographic changes related to different treatment strategies did not reveal differences between the combination of two DMARDs plus initial GCs with a biologic agent plus methotrexate (MTX) (14). The percentage of annual radiographic progression was calculated to be reduced by 0.54% ($p<0.00001$) in the GC group compared to placebo (14). This was also clearly shown in the BeSt (Behandel Strategieen) study in which comparable outcomes were found for treatment arm 3 (DMARD combination treatment with initial dose of 60 mg prednisone daily) and treatment arm 4 (infliximab plus methotrexate) (15, 16).

Dosage schedules providing inhibition of radiographic joint damage

Among different dosage schedules used in randomised clinical trials, two main types can be distinguished for oral GC use: The first type is a constant dose of 5 to 10 mg prednisone or prednisolone/day over 2 years; the second type is a fairly high initial dose of prednisolone tapered to zero within 6 to 8 months.

The first type is found in the majority of the randomised studies:

- In the pivotal trial, 7.5 mg prednisolone/day was used without any restriction to other treatments (3). In the 106 patients evaluated for radiological changes, a mean 2-year-progression of 0.72 Larsen units in the GC group compared to 5.37 Larsen units in the placebo group. However, the placebo group had a more severe disease with a mean of 6.23 Larsen units at baseline *versus* (*vs*.) 2.65 Larsen units in the GC group.
- In the Utrecht trial (17), 10 mg prednisone/day were given in the GC group, non-steroidal anti-inflammatory drugs (NSAIDs) were allowed. After 6 months, sulfasalazine (SSZ) could be given as rescue medication (as was done with nearly half of the patients in the GC and in the placebo group). Mean changes from baseline in modified Sharp scores [van der Heijde modification of the Sharp method (SHS)] were 8 *vs*. 15 at 12 months and 16 *vs*. 29 at 24 months, respectively. The inhibition of radiographic joint damage persisted for an additional 3 years of followup (18).
- In the BARFOT study (5), 7.5 mg prednisolone/day were given in the GC group together with DMARDs (50% MTX, 35% SSZ). At 2 years, the median change in total Sharp score was 1.8 for the GC group and 3.5 for the placebo group. In the GC group, 25.9% of the patients had radiographic progression compared with 39.3% in the control group.
- In the LDPT (Low-Dose Prednisolone Therapy) study (7), patients in the GC group received 5 mg prednisolone/day with background DMARD (gold sodium thiomalate or MTX). After 2 years, the least squares mean difference between the placebo and the GC group was 3.14 for the Ratingen score and 7.20 for the SHS.
- The CAMERA-II (Computer-Assisted Management of Early Rheumatoid Arthritis–II) trial showed that 10 mg prednisone/day added over two years to an MTX based tight control treatment strategy increased effectiveness and outcome (*i.e*. erosive joint damage) without increasing toxicity (19).

The second type of GC schedule, with a fairly high initial dose of prednisolone tapered to zero in 6-8 months, was first published in the COBRA (Combinatietherapie Bij Reumatoide Artritis) trial and later seen in the BeSt and CARDERA (Combination of Anti-Rheumatic Drugs in Early RA) trials:

- According to the COBRA protocol (20), patients started with 60 mg prednisolone/day tapered over 28 weeks to 0 mg, together with 7.5 mg MTX/week and 2 g SSZ/day. In the control group, patients were treated with 2 g SSZ/day. At 1 year, the median of the Sharp score had increased significantly less in the GC (6.5) *vs*. the SSZ only group (17). Even after 4-5 years of follow-up, the radiologic progression was superior in the GC treated group: 5.6/year *vs*. 8.6/year, respectively (21).
- In the BeSt study (15), 133 patients of group 3 started with 60 mg prednisolone/day tapered within 7 weeks to 7.5 mg/day, thereafter tapered to 0 in 28 weeks, in case of DAS44 ≤2.4. 7.5 mg MTX/week and 2 g SSZ/day were given as DMARDs. After 1 year, the median of progression in radiographic joint damage (total SHS) was 1.0 in group 3, 0.5 in group 4 (infliximab + MTX), 2.0 in group 1 (sequential monotherapy), 2.5 in group 2 (step-up combination therapy) (significant for groups 1 and 2 *vs*. groups 3 and 4). In the following 4 years, the annual progression was comparable across groups (16).

Table I. Randomised controlled trials with low to medium doses of glucocorticoids in early rheumatoid arthritis.

Author/study	Disease duration (yr) mean/median	Glucocorticoid group	Treatment targeted towards remission?	Control group	Clinical outcome for the GC group compared to the control group	Radiographic outcome for the GC group compared with the control group
Kirwan / ARC 1995 (3)	1.3	7.5 P mg/d over 2 years	No	Placebo	At 3 months, more reduction in pain score, disability score, articular index; no difference after 2 years	After 2 years, +0.72 *vs*. +5.37 Larsen units (mean)
Boers *et al*. COBRA 1997 (20)	0.3	60 mg P/d tapered in 28 weeks, 7.5 mg MTX/w and 2 g SSZ/d	No	Placebo, 2 g SSZ/d	At 1 year, more reduction in DAS 28; no difference in functional disability	After 1 year, median of the Sharp score 6.5 *vs*. 17
van Everdingen *et al*. Utrecht study 2002 (17)	<1	10 mg P/d over 2 years, NSAID, after 6 months 2 g SSZ possible as rescue	No	Placebo, NSAID, after 6 months 2 g SSZ possible as rescue	More improvement in the first 6 months; at 24 months, no difference except for 28-joint score of tenderness	At 12 months, mean change in Sharp score 8 *vs*. 15; at 24 months, 16 *vs*. 29, respectively
Capell *et al*. WOSERACT 2004 (11)	1.0	7 mg P/d over 2 years, 40 mg SSZ/ kg	No	Placebo, 40 mg SSZ/ kg	At 1 year, modified ACR 20 53% *vs*. 43%; no difference after 2 years	No difference after 1 or 2 years
Svensson *et al*. BARFOT 2005 (5)	0.5	7.5 P/d over 2 years, DMARDs for all patients, 50% MTX, 35% SSZ	No	Placebo, DMARDs for all patients, 53% MTX, 37% SSZ	At 2 years, 55% remission *vs*. 33%	At 2 years, increase in total Sharp score 1.8 *vs*..3.5
Wassenberg *et al*. LDPT 2005 (7)	0.75	5 mg P/d, DMARD (i.m. gold, MTX)	No	Placebo, DMARD (i.m. gold, MTX)	Clinical and functional outcome tended to be better (not significantly)	Least square mean difference 3.14 for the Ratingen score and 7.20 for the SHS.
Goekopp-Ruiterman *et al*. / the BeSt Study 2005 (15)	0.5	Group 3: 60 mg P/d tapered in 7 weeks to 7.5 mg/d; tapered to zero after 28 weeks, in case of DAS44 ≤ 2.4; 7.5 mg MTX/w, 2000 mg SSZ/d	Yes	Group 1: sequential monotherapy Group 2: step-up combination therapy Group 4: MTX + Infliximab	After 1 year, DAS44 ≤ 2.4 in 71% of group 3, 74% of group 4, 64% of group 2, 53% of group 1	After 1 year, median of the progression in radiographic joint damage (total SHS): 1.0 in group 3, 0.5 in group 4, 2.0 in group 1, 2.5 in group 2 (significant for groups 1 and 2 *vs*. groups 3 and 4).
Bakker *et al*. CAMERA II trial 2011 (19)		10 mg P/d over 2 years, MTX-based tight control strategy	Yes	Placebo, MTX-based tight control strategy	After 2 years, 72% *vs*. 61% sustained remission, lower proportion (14% *vs*. 36%) needed biological treatment	Less erosive joint damage
Choy *et al*. (CARDERA) 2008 (22)	<2	60 mg P/d tapered to 0 over 34 weeks, MTX or MTX + cyclosporine	No	MTX or MTX + cyclosporine	At 2 years, improved DAS 28	At 2 years, increase in Larson score 3.83 *vs*. 5.95
Möttönen *et al*. FIN-RaCo 1999 (23)	0.5–0.6	5-10 mg P, 7,5-15 mg MTX/w, 1-2 g SSZ/d, 300 mg HQC/d	Yes	Placebo, 2-3 g SSZ/d, 0–10 mg P/d	At 1 year: 24/97 *vs*. 11/98 in remission, 75% *vs*. 60% ACR 50	Larson-Score at baseline and at 2 years: 2 and 4 *vs*. 2 and 12, respectively
Grigor *et al*. TICORA 2004 (26)	1.6	120 mg triamcinolone intraarticular or intramuscular every 4 weeks within the first 3 months of starting a new DMARD	Yes	Routine care	At 18 months, DAS44 -3.5 v*vs*. -1.9; improved HAQ; 65% *vs*. 16% in remission	At 18 months, median of the total Sharp score: +4.5 *vs*. +8.5

d: day, w: week; P: predniso(lo)ne; GC: glucocorticoid; NSAID: non-steroidal anti-inflammatory drug; MTX: methotrexate; SSZ: sulfasalazine; HCQ: hydroxychloroquine; DAS: disease activity score; SHS: van der Heijde modification of the Sharp method; HAQ: health assessment questionnaire.

- In the CARDERA study (22), 231 patients received 60 mg prednisolone/day tapered to 0 mg over 34 weeks together with MTX or MTX + cyclosporine. At 2 years, the mean change in Larsen score was 3.83 in the GC group *vs*. 5.95 in the control group.

In a third type of trials, the main focus was set on different treatment strategies which included GC use in different schedules. Therefore, the effect of

GCs cannot be separated well from the effects of other measures. The COBRA study and the BeSt trial need to be mentioned in this context as well.

- In the FIN-RACo (Finnish Rheumatoid Arthritis Combination Therapy) trial (23), the combination treatment group received 5-10 mg prednisolone/day in addition to 7.5–15 mg MTX/week, 1–2 g SSZ/day and 300 mg hydroxychloroquine/day. In the single-treatment group, patients were treated with 2-3 g SSZ daily and optional 0–10 mg prednisolone/day (63/98 patients). At 2 years, the median Larsen score had increased from 2 to 4 in the combination group and from 2 to 12 in the single-treatment group, respectively. [The clinical and radiological difference persisted after 5–11 years (24, 25)].
- In the TICORA (Tight Control of Rheumatoid Arthritis) trial (26), the intensive care group underwent a tight control protocol with visits every 4 weeks. A total dose of 120 mg triamcinolone was given every four weeks intra-articularly (i.a.) or intramuscularly (i.m.), within the first 3 months of starting a new DMARD, according to a protocol of escalation. The control group received routine care. At 18 months, the differences in the median of the total Sharp score changes were +4.5 *vs*. +8.5, respectively.

Overall, there is good evidence for a beneficial radiographic effect of GCs for: a) 5–10 mg prednisolone/day over 2 years; b) 60 mg prednisolone initially, tapered to low-dose prednisolone or zero over 6–8 months and c) 120 mg triamcinolone, parenterally (i.a. or i.m.) given every 4 weeks. In these trials, short-term symptomatic benefit was associated with less radiographic progression (27).

Frequently used dosage schedules lacking evidence to provide inhibition of radiographic joint damage

In daily routine rheumatological practice, high doses of GCs, *e.g*. 60 mg prednisolone/day as proposed by the COBRA protocol, are only rarely used. Usually, a low- to moderate-dose GC schedule is thought to provide sufficient benefit (28). Following the EULAR recommendations (10), the dose is often tapered as rapidly as clinically feasible. Even very low dosages (1–4 mg prednisolone/day) are adequate in many situations (8).

The total dose of GCs may be quite varying between different dosage schedules: With a dose of 5 mg prednisolone/day for 2 years as used in the LDPT study (7), the total dose after 2 years is 3650 mg prednisolone. This compares to 5475 mg prednisolone in 2 years for the BARFOT study, using 7.5 mg prednisolone/day (5). In GC schedules tapering the daily dose rapidly, the total amount of prednisolone may be much less. In the COBRA study (60, 40, 25, 20, 15, 10 mg prednisolone/day for week 1, 2, 3, 4, 5, 6, respectively, then 7.5 mg daily for 6 more weeks) (20), the cumulative dose of prednisolone was 1505 mg. Dosage schedules with a low (or even very low) to moderate GC dose initially and tapering after onset of the DMARD effect may use no more than 500–1000 mg prednisolone totally (*e.g*. 7.5 mg daily initially for 6 weeks, then 5 mg for 6 weeks, 2.5 mg for 6 weeks amount to 630 mg prednisolone).

For lower dosage schedules that are well in accordance with the EULAR recommendations (10), there is no evidence whether they have a disease-modifying effect comparable to cumulative doses of 1500–5000 mg prednisolone. On the other hand, with the common implementation of "treat to target" strategies (29), including higher initial doses of DMARDs and a more rapid dose escalation, the percentage of patients taking advantage from a concomitant GC treatment, especially in medium or high doses or taken over a long period, may diminish. Thus, within a "treat to target" setting, lower dosages of prednisolone may be possible and render sufficient disease modification.

Adverse effects of glucocorticoid treatment in rheumatoid arthritis

Possible adverse effects of moderate- to high-dose GC treatment remain a cause of reluctance with the use of GCs for patients and physicians. The rate of adverse events of low- to medium-dose oral GCs in RA patients is thought to be 43 per 100 patient years, mostly psychological and behavioural disturbances, followed by dermatological and cardiovascular events as well as gastrointestinal adverse reactions (30). There are conflicting results concerning osteoporotic fractures: in the Utrecht study an increase in vertebral fractures was documented – a finding that has not been seen in other studies (31). The 2006 review by Da Silva *et al*. (32) came to the main conclusion "that definitive associations of low dose GC with many adverse effects remain elusive" but that "the balance of risks and benefits of low-dose treatment clearly differs from that of medium and high-dose treatment, for which the mechanism of action of GC may be different."

Therefore, according to EULAR recommendations (33), standard care monitoring needs not be extended for RA patients with low-dose GC therapy, except for osteoporosis and assessments for ankle oedema, blood glucose and glaucoma. For patients with a GC treatment of 7.5 mg prednisolone daily or more for at least 3 months, calcium and vitamin D supplementation and an antiresorptive therapy with bisphosphonates need to be considered [see article in this Supplement on glucocorticoid-induced osteoporosis]. Appropriate gastro-protective medication should be given in case of intake of NSAIDs (34).

Summary

GCs are potent drugs to reduce signs and symptoms of inflammation in RA. Moreover, both, a low-dose GC treatment over 2 years and a treatment schedule with high starting doses followed by rapid tapering have been shown to be disease-modifying. If low or medium GC doses tapered as rapidly as clinically feasible - as recommended by EULAR - have a disease-modifying effect, has still to be investigated.

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