Glucocorticoids in the treatment of rheumatoid arthritis

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ABSTRACT

Glucocorticoids (GC) are now being used for over 65 years in the treatment of rheumatoid arthritis (RA). There is by now good evidence for their disease modifying effect, especially in early RA. When used in a dosage of 7.5–10 mg most adverse effects can be quite well handled, though monitoring and awareness for infections are important. The CAMERA II study is discussed, in which patients with early RA were treated with a tight control scheme of climbing dosages of methotrexate plus either 10 mg prednisone daily or placebo. After the two years of the trial, 70 % of the patients treated with tight control strategy without GC had no erosions versus 82% of the patients treated with additional prednisone. Remission was reached more often and earlier on in the strategy with prednisone compared to the strategy with placebo. It may be suggested that GC have a greater beneficial effect on joint structure than can be explained by their anti-inflammatory effects only.

Glucocorticoids (GC) were used in a rheumatoid arthritis (RA) patient for the first time in 1948, with an impressive effect, leading to the Nobel prize for Medicine to Kendall, Reichstein and Hench in 1950 (1). These "preliminary results" led to intemperate and unscientific extremes of exaggerated praise, bitter denunciation and emotion-laden criticisms. Though some of the emotions around the use of GC have now been tempered, finding the right balance between advantages and disadvantages still is a matter of debate (2). GC have now reached 65 years of age, but they are not allowed to retire yet, and probably never will. Information from European databases indicates that about half of all RA patients even now is using concomitant GC therapy for a more prolonged period of time, nearly all in dosages below 7.5 mg of prednisone equivalent/day (3). Generally spoken the balance between efficacy and adverse events is a favourable one at and below this dosage.

In 2007 a Cochrane review was published regarding the disease-modifying effect of GC in patients with RA (4). In all but one trials in RA patients in which GC were compared to placebo, GC significantly retarded the progression of erosions, assessed after one as well as after two years duration of therapy. Remarkably, in different studies it was reported that this retardation of erosion progression persisted, even years after stopping the GC (5, 6); this effect has not been shown for any other disease modifying antirheumatic drug (DMARD). It may be suggested that GC have a greater beneficial effect on joint structure than can be explained by their anti-inflammatory effects only.

Adverse events of low dose glucocorticoids are well known, but have to be evaluated in the context of the treated inflammatory condition. Chronic inflammation increases the risk of cardiovascular diseases, of infections, of insulin-resistance, of inflammatory bone loss and other comorbidities. Reducing these risks by reducing chronic inflammation may in some way counterbalance the negative effects of GC; GC are so to say a double edged sword (3). For instance, oral glucose tolerance tests showed an increased area under the curve of blood glucose as well as C-peptide in patients with RA compared to healthy controls, but no difference between RA patients on longstanding GC treatment and RA patients naïve for GC treatment was observed (7).

We are now able to manage many of the reported adverse events of GC, e.g. preventing bone loss by prophylactic treatment with bisphosphonates, calcium and vitamin D. The clinically most important adverse effect to deal with is the increased infection risk; especially in the elderly population a dose-related increase in infections is reported among patients using GC, with an odds

ratio (OR) of 1.72–2.26, depending on actual dosage and duration of GC use (8). This increased risk is strongly influenced by additional risk factors, such as higher age of the patients (>60 years), chronic lung or renal disease, low physical function, history of serious infection and concomitant other medication (9). Also because signs and symptoms of infection may be blunted by the use of GC, a high rate of suspicion and, if needed, monitoring for infections in patients on chronic GC treatment are important (10). From a large observational cohort study in the UK it has become evident that low to medium dosages of GC are associated with an increase in heart failure (OR 1.18, confidence interval (CI) 1.05-1.33), but NOT with myocardial infarction, stroke, transient ischemic attack or cardiovascular mortality (11). The relative risk for cardiovascular events in patients taking high dosages of GC, however, was 2.56 (CI 2.18–2.99).

Tight control treatment of patients with RA, especially early RA, is strongly promoted, based on insight into the disease process ("window of opportunity"), based on the results of different clinical trials and on consensus meetings (12). One of the studies that clearly confirmed the superior value of tight control was the CAMERA (Computer Assisted Management in Early Rheumatoid Arthritis) study, performed in the region of Utrecht, the Netherlands. In this study all patients were treated with the same drug treatment aiming at remission (step-up methotrexate (MTX) therapy, to which cyclosporine was added in case of inefficacy), but they were randomised to one of two treatment strategies: tight control (evaluation every month, and in case of inadequate improvement increase in treatment, and in case of remission reduction in treatment; the decision determined with a computer program) *versus* usual care at that time (evaluation every three months, increase or decrease dependent on the judgement of the treating rheumatologist, albeit aimed also at remission) (13).

The second CAMERA study (CAMERA II) performed in the same Utrecht region has recently been published. In this double-blind randomised study, all patients were treated with the computer guided monthly tight control scheme, aiming for remission with increasing dosages of MTX, but randomised to addition of 10 mg prednisone daily or of placebo from start for the whole study duration of 24 months (14). All patients had early RA according to the ACR 1987 criteria, with a disease duration less than one year, and all were DMARD and GC naïve. Treatment was started with MTX 10 mg/week, if necessary the dose was increased every month with 5 mg up to 30 mg/week; if no remission was reached at the maximum MTX dose, adalimumab 40 mg/2 weeks was added. In addition either 10 mg prednisone or placebo was added from start of the trial. When remission was present for more than 3 months, the treatment was reduced, first the MTX. The definition of remission that was used in both CAMERA studies was: no swollen joints and *2 out of the following 3*: tender joints 3 or less, ESR 20 or less, VAS general health (0-100 mm, 100 being the worst score) 20 or less. Randomised were 236 patients, of whom 60 % was woman; mean age was 54 years; 68% of patients was rheumatoid factor positive; the mean ESR was 35 mm; patients had a mean of 16 tender and 15 swollen joints. Primary outcome was the Sharpvander Heijde erosion score at the end of the two years; this primary outcome was statistically significantly in favour of the GC group. Importantly, after the two years of the trial, 70% of the patients treated with tight control strategy without GC had no erosions *versus* 82% of the patients treated with additional prednisone. As expected, clinical variables, as well as CRP and ESR improved during the first 6 months more in the strategy with GC than in the strategy without GC; after 6 months the variables were similar in both groups, as a consequence of the continued striving for remission. ACR 50% response after 1 year and ACR 70% response after two years were significantly better in the prednisone treated group. Remission during at least 3 months was reached at least once in 72% of patients in the strategy with GC *versus* 61% of those in the strategy without GC; the start of the first remission occurred earlier in the prednisone group (6 *vs*. 11 months from start of the trial). If oral MTX was not well tolerated, or not leading to remission, MTX was given subcutaneously (sc); if thereafter remission was not reached, adalimumab was added as an additional step. In the prednisone group only 26 patients needed sc MTX *versus* 60 in the placebo group; the difference in use of the biological was even more impressive: 42 in the strategy group with placebo needed it *versus* only 16 in the strategy group with prednisone. The more remarkable is the favourable result in erosion score in the latter group. A detailed register of adverse events was kept at each monthly visit; in the prednisone strategy group, there was no increase in infections, cardiovascular events, new diabetes mellitus, new hypertension or fractures. There were significantly less gastrointestinal adverse effects in the prednisone strategy group compared to the placebo strategy group, especially nausea (reported at least once during the trial by 23 patients *versus* 43 patients, respectively), and remarkably less liver enzyme disturbances (ALAT above upper limit of normal): assessed at least once during the trial in 15 patients *versus* 33 patients, respectively. GC seem to improve the gastrointestinal tolerance of MTX; this could have been due to less NSAID use in the prednisone group because of lower disease activity (as we demonstrated in our earlier Utrecht study, in which we compared the effects of GC with those of placebo in early RA (15)), and also to less use of MTX in the prednisone group although the difference was small: mean weekly MTX dosage in the prednisone strategy group 20 mg, *versus* 23 mg in the placebo strategy group. A third explanation could be direct interaction between GC and MTX at the cellular level, as has been suggested in in-vitro studies (16).

With regard to adverse events on bone, we measured bone density with DEXA and monitored for (peripheral) fractures (17). We did not find any difference between the prednisone strategy group and the placebo strategy group. In fact bone mineral density increased

significantly in both groups, but we treated all patients with daily calcium and vitamin D and the bisphosphonate alendronate 70 mg/week, according to Dutch guidelines (18).

Patients on GC often worry about weight gain. Indeed, in the CAMERA II study patients in the prednisone strategy group gained more weight than those in the placebo strategy group (mean 2.9 kg *versus* 1.3 kg; p=0.03). Data were analysed with a longitudinal regression (mixed model) analysis with BMI as the dependent variable and treatment strategy and DAS28 as independent variables, correcting for baseline BMI and possible confounders (sex, age, and rheumatoid factor status) (19). No independent association was found of GC therapy with a change in BMI, but a lower DAS28 was associated with an increased BMI 6 months later. Clinical cut-off points showed a clear association between DAS28 level and the change in BMI 6 months later. Weight gain during treatment with prednisone in early RA thus seems attributable to a reduction of disease activity and is probably, at least partly, regaining weight that was lost when the RA was not yet adequately treated.

In conclusion, GC have a clear DMARD effect in early RA; a starting dosage ranging from 7.5 to 10 mg prednisone equivalent seems best regarding efficacy as reported in literature and the balance between efficacy and safety. Adverse effects tend to be overestimated; the clinically most relevant adverse event is the increase in infection rate, especially in elderly patients. It may be suggested that GC have a greater beneficial effect on joint structure than can be explained by their anti-inflammatory effects only. Uncoupling of disease activity and joint damage has been reported to occur during treatment with TNF alpha blockers; this might also be the case for treatment with GC.

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