Low-dose glucocorticoid therapy in rheumatoid arthritis. A review on safety: published evidence and prospective trial data

José AP da Silva, Johannes W.G. Jacobs, John R. Kirwan, Maarten Boers, Kenneth G. Saag, Luis B.S. Inês, Eelco J.P. de Koning, Frank Buttgereit, Maurizio Cutolo, Hilary Capell, Rolf Rau and Johannes W. J. Bijlsma

Ann. Rheum. Dis published online 26 Aug 2005;
doi:10.1136/ard.2005.038638

ARD Online First, published on August 26, 2005 as 10.1136/ard.2005.038638

Low-dose glucocorticoid therapy in rheumatoid arthritis.

A review on safety: published evidence and prospective trial data.

José A. P. Da Silva, Johannes W. G. Jacobs, John R. Kirwan, Maarten Boers, Kenneth Saag, Luís B. S. Inês, Eelco J.P. de Koning, Frank Buttgereit, Maurízio Cutolo, Hilary Capell, Rolf Rau, Johannes W. J. Bijlsma.

Authors' titles and affiliations.

José A. P. Da Silva, MD, PhD, Professor of Rheumatology, Reumatologia, Hospitais da Universidade de Coimbra, Portugal.
Johannes W.G. Jacobs, MD, PhD, Associate Professor, Dept. of Rheumatology and Clinical Immunology, University Medical Center Utrecht, The Netherlands.
John R. Kirwan BSc, MD. University of Bristol Academic Rheumatology Unit, Bristol Royal Infirmary, Bristol, UK.
Maarten Boers, MSc, MD, PhD, Professor of Clinical Epidemiology. Department of Clinical Epidemiology and Biostatistics, VU University Medical Center. Amsterdam, The Netherlands.
Kenneth G. Saag, M.D., M.Sc. Associate Professor, Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, U.S.A.
Luis B.S. Inês, MD, Reumatologia. Hospitais da Universidade de Coimbra, Portugal.
Eelco J.P. de Koning, MD, Leiden University Medical Center, Depts. of Nephrology and Endocrinology, Leiden, The Netherlands.
Frank Buttgereit, MD, Professor of Rheumatology, Charité Universitätsmedizin Berlin, Germany.
Maurizio Cutolo, MD, Professor of Rheumatology, Research Laboratory and Division of Rheumatology, Department of Internal Medicine, University of Genova, Italy.
Hilary Capell, MD, Centre for Rheumatic Diseases, Royal Infirmary Glasgow, Scotland.
Rolf Rau, MD, PhD, Department of Rheumatology, Evangelisches Fachkrankenhaus, Ratingen. Germany.
Johannes W. J. Bijlsma, Professor and Head, Dept. of Rheumatology and Clinical Immunology, University Medical Center Utrecht, The Netherlands.

Contact Address:
José A.P. Da Silva.
Reumatologia. Hospitais da Universidade.
300-075 Coimbra.
Portugal
e-mail: jdasilva@ci.uc.pt

Running Title:
Safety of low-dose glucocorticoids in RA

Key words:
Glucocorticoids. Low-dose. Toxicity. Safety. Rheumatoid arthritis. Adverse-effects. Side-effects. Corticosteroids. Steroids. Prednisone. Prednisolone. Review.

Word count: With abstract and tables, but without title page and references: 6064

Abstract

Objective: To assess the incidence and severity of adverse-effects of long-term low-dose glucocorticoid therapy in rheumatoid arthritis.
Materials and methods: We reviewed the literature of clinical trials and physiological studies evaluating adverse effects of glucocorticoids. In addition, safety data from four prospective, randomised, placebo-controlled clinical trials of two years duration evaluating the effect of low-dose glucocorticoids (≤10mg prednisone equivalent per day) in patients with mainly active, early rheumatoid arthritis was evaluated. Results from the COBRA trial, which used higher doses for a short period of time, followed by 5 months low dose, are also analysed.
Results: Adverse-effects of glucocorticoids are abundantly referred to in literature. However, in the available literature on low-dose glucocorticoid therapy very little of the commonly held beliefs about their incidence, prevalence and impact of GC proved to be supported by clear scientific evidence. Additional data from the randomised controlled clinical trials reviewed showed that the incidence, severity and impact of adverse effects of low dose glucocorticoid therapy in rheumatoid arthritis trials are modest, and often not statistically different to those of placebo.
Conclusions: Probably many of the well known adverse effects of glucocorticoids are predominantly associated with high dose treatment. Given the lack of sound evidence, the use of low-dose glucocorticoids in rheumatoid arthritis merits reconsideration, weighing the risks and benefits. Further studies designed to address safety of chronic low-dose glucocorticoid treatment in rheumatoid arthritis are warranted to establish the true incidence, severity and impact of adverse-effects.

Introduction

The introduction of glucocorticoids in the 1950's has been a revolution in the treatment of a large variety of inflammatory diseases. Enthusiasm generated by the dramatic results led to the use of high doses, which revealed a spectrum of toxicity that shook the foundations of this therapy. Despite this, glucocorticoids (GC) still play a pivotal role in the management of diverse rheumatic conditions. The proportion of patients treated with GC by practicing physicians on a daily basis is clearly in excess of the usually conservative recommendations in textbooks and review papers. Recent studies demonstrating the disease modifying potential of GC in lower dosages in rheumatoid arthritis (RA) have renewed the debate on risk/benefit ratios with this therapy. Arguments against GC use are dominated by fear of a toxicity spectrum that is well engraved in international medical culture but which is strongly influenced by observations derived from the use of high doses of GC. Whether these fears are justified in relation to lower dose therapy, specifically for patients with RA, remains incompletely answered.

To address this problem, a working party was organized, comprising experts with a special interest in this area, including rheumatologists and one endocrinologist from Europe and the U.S.A. with representation of most groups that have conducted randomised clinical trials on the use of GC in RA. The panel agreed to perform two major tasks of which the results are presented in this paper:

1. A literature review of the adverse-effects of long-term low-dose GC especially in rheumatic diseases. The group composed an extensive and comprehensive list of all putative adverse-effects attributed to GC on a primary search of textbooks and review papers. This list was categorized in sections similar to those in this text. As a first step, for each category a thorough search was performed, using the adverse-effects as key-words and the reference lists of the original papers. This literature was reviewed and described; the texts produced circulated numerous times among all members of the group for critical appraisal of completeness and balance. Given that the vast majority of available data on GC is observational and retrospective, regarding diverse diseases, dosages and regimes, appreciation of the level of evidence was frequently difficult and subjective. This then was resolved by reviewing the underlying data and discussion, until consensus was achieved.
2. An analysis of toxicity data from the randomised controlled trials of GC in RA. As the working party comprised of representatives of all groups which conducted two-year trials on the use of GC in RA, very detailed information on adverse-effects from these trials was available for the discussions. Differences in methodology precluded a systemic meta-analysis of the adverse-effects observed. Here results from each trial, where available, are summed. Trials of which data is incorporated in this review include the Arthritis and Rheumatism Council low-dose glucocorticoid study, here further designed as ACR-study,[1,2] the German study, here further designed as LDPT-study,[3] the Utrecht study,[4] and WOSERACT,[5] see Table 1. Although the proposed definition of 'low-dose' is 7.5 mg prednisolone equivalent or less, to enhance readability these four trials as a group are in this paper designed as 'the four extensively reviewed trials on low-dose GC in RA'. More details on these trials are available via hyperlinks to the electronic version of this article on the website of Annals of the Rheumatic Diseases (Hyperlink 1). Previously unpublished detailed monitoring results from the "combination therapy in early rheumatoid arthritis" (COBRA)-trial are included in the web version of this paper (Hyperlink 2).

This paper is the result of these efforts. It gives a critical and pragmatic overview of scientific evidence on the adverse effects of chronic GC therapy in lower dosages (10 mg prednisolone equivalent or less) in RA in daily clinical practice.

Table 1. Characteristics of the four extensively reviewed rheumatoid arthritis trials using ≤10 mg prednisone daily

Study	**ARC-study**	**LDPT-study**	**Utrecht study**	**WOSERACT**
Year of publication	1995	2002	2002	2004
Reference	1,2	3	4	5
RA duration at entry	< 2 years	< 2 years	<1 year	median 12 months
Number of patients,. prednisolone group	61	34	40	84
Prednisolone dose / day	7.5 mg	5 mg	10 mg	7 mg
Duration of trial	2 years	2 years	2 years	2 years
Associated DMARDs	various	i.m. gold or MTX	Sulfasalazine rescue	Sulfasalazine

Musculoskeletal adverse-effects

Osteoporosis

Osteoporosis is a well established side effect of chronic GC use. The incidence of osteoporosis is time and dose dependent, but there is no consensus regarding a "safe" dose. Although some studies suggest that doses of 7.5 mg of prednisone per day or less are relatively safe, a longitudinal study observed an average loss of 9.5% from spinal trabecular bone over 20 weeks in patients exposed to 7.5 mg of prednisolone per day.[6-8]. Studies focused on low-dose therapy are relatively scarce, however. Further, it is important to recognize that in non-randomised studies, factors such as age, underlying disease, disease severity, co-medication and duration of treatment can lead to confounding by indication for GC, and may thus preclude definite conclusions. Alternate-day GC regimes have not been demonstrated to reduce bone loss.[9,10]

In 1997, an exhaustive literature search for all prospective studies found only 18 studies and 329 patients in which bone mass was studied prospectively while on GC treatment for any disease.[11] An update of this review now includes almost 1200 patients.[12] At a mean dose of almost 9 mg prednisone equivalent /day, the best estimate of bone loss overall in spine and hip (without bisphosphonate therapy) is 1.5% per year. Important positive predictive factors include starting dose and chronic usage; and in the spine, dose and lack of vitamin D supplementation.

The consequences of this bone mass loss upon fracture rate proved to be quite significant. Though the underlying disease itself, such as RA may be associated with an increased incidence of osteoporosis or falls, the chronic use of GC further amplifies this increased risk by a factor 2.[13,14] In a recent multicenter cross-sectional study, 205 patients with RA who were receiving GC orally on a daily basis were compared with 205 matched patients who did not receive GC. Vertebral deformities were found in 25% of patients on GC versus in 13% of controls. The occurrence of vertebral deformities was dose dependent.[7]

In a recent retrospective cohort study using the General Practice Research Database of the UK it was shown that the rate of clinical vertebral fractures increased by 55% for a dose of prednisolone of less than 2.5mg/d and by over 400% if the dose exceeded 7.5 mg/day.[15] Inflammatory disease activity has been shown to be an independent risk factor for osteoporosis, at least in RA. Disease activity leads to reduced physical activity and elevated levels of inflammatory cytokines, such as TNFα, which stimulate differentiation of osteoclasts both directly and indirectly via rank ligand (osteoclast differentiation factor) and thus to bone loss. It is, therefore, possible that GC in RA, leading to decreased disease activity, may cause less bone loss than they would have in the absence of inflammatory disease. Studies conflict as to whether cumulative dose is,[8,16] or is not[15,17] associated with the degree of bone loss. A recent study showed that the greatest increase in the risk of vertebral fractures induced by GC was observed in older postmenopausal women, age being a risk factor independent from BMD.[18]. On the other hand, it is quite likely that, like some studies suggested, fractures occur at less decreased BMD levels in GC-treated patients than in patients not treated with GC.[19]

Data from the four extensively reviewed trials on low-dose GC in RA show that BMD loss over 2 years of low dose prednisone was not significantly different from placebo (See hyperlink 1). The higher doses of prednisone used in the COBRA-study was associated with a higher BMD loss,[20] but this did not reach statistical significance either (See Hyperlink 2). Fracture incidences were similar in both groups in the LTDP study.[3] Despite this, the Utrecht group found a double incidence of radiological vertebral fractures in the prednisone group, but this did not reach statistical significance.[4]

Osteoporosis is probably the most common adverse effect of chronic low-dose GC but fortunately is preventable. Strategies for the prevention and treatment of GC-induced osteoporosis are well established and have been object of recent extensive reviews,[19,21,22] and authoritative guidelines.[23-25]

Osteonecrosis

Osteonecrosis (avascular necrosis of bone) has been, for a long time, considered an important consequence of high dose GC use. In a Japanese study of osteonecrosis of the femoral head, 35% of all cases were related to GC treatment.[26] However, it is sometimes difficult to differentiate whether the treatment or the underlying disease is the cause, as some conditions, such as systemic lupus erythematosus (SLE), are associated with increased risk on osteonecrosis,[27] especially in young patients with multi-organ involvement. This is one of the reasons why some authors question the evidence that GC are actually responsible for osteonecrosis.[28] Although the occurrence of GC-related osteonecrosis seems to be dose-dependent, this might be confounded by the fact that higher dosages are related to more severe underlying disease and increased risk of osteonecrosis. One study reported osteonecrosis in 2.4% of patients receiving GC replacement therapy,[29] but data on low-dose GC treatment is scarce and mostly anecdotal. At least in SLE, higher average dose may be a more important predictor of avascular necrosis of bone then cumulative dose.[30]. No case of avascular necrosis was observed in the four extensively reviewed trials on low-dose GC in RA nor in the COBRA-trial (See Hyperlink 1 and 2).

Many crucial questions in this area remain unanswered, namely regarding the relevance of the dose, route of administration and duration of GC treatment, as well as the host factors that modulate the risk. In the meantime, it is generally accepted that in patients treated with low dosages of GC, osteonecrosis is very infrequent. Primary prevention is not really possible; awareness should be increased.[31]

Myopathy

The most remarkable finding when searching the literature regarding this topic is the lack of data and proper studies. A recent review on this subject supports this contention.[32] Based on the scarce information available and our own experience, we believe that myopathy is exceedingly rare with glucocorticoid doses below 7.5 mg prednisolone-equivalent daily. Chronic steroid myopathy is quite often suspected, but infrequently found and/or documented. The clinical picture can be difficult to distinguish from the effects of the underlying disease, especially in case of musculoskeletal conditions, such as myositis or inflammatory arthritis.[33] On EMG examination there is an absence of spontaneous electrical activity; the serum aldolase and CK-level are normal, but creatinuria may be increased. These findings are considered suggestive of steroid myopathy.[34] Diagnosis can be ascertained by muscle biopsy, showing atrophy of type II fibres, and absence of inflammation. There are no real prevention or individual risk factors to be valued; awareness will facilitate early recognition of this problem. No cases of myopathy were observed in the four extensively reviewed trials on low-dose GC in RA (hyperlink 1).

Endocrine and metabolic adverse-effects

Glucose intolerance and diabetes

GC increase serum glucose levels via an increase in hepatic glucose production and changes in insulin production and resistance.[35-40] In patients without pre-existing

abnormalities of glucose tolerance, GC will result in slightly increased fasting glucose levels and a more pronounced increase of postprandial values. The increment follows a similar pattern in diabetic patients but tends to be more pronounced in long-standing diabetes.[41,42]

Glucocorticoid-related hyperglycemia is dose-dependent. However, low-dose GC are not devoid of this effect. One case-control study suggested an increased risk (odds ratio 1.8) for initiation of anti-hyperglycemic drugs during glucocorticoid therapy using 0.25-2.5 prednisone equivalent per day.[43]. Hyperglycaemia can also be observed after intra-articular GC.[44] It is likely that subjects with risk factors for the development of diabetes mellitus, such as a family history of this disease, increasing age, obesity and previous gestational diabetes mellitus, are at increased risk to develop new-onset hyperglycaemia during GC therapy.[41]This is usually rapidly reversed upon GC cessation, but some patients will go on to develop persistent diabetes.[45]

Next to the average daily dose, the type of GC is of great importance. Dexamethasone is 30 times and prednisone 4 times as potent as hydrocortisone in the impairment of glucose metabolism[46]. The suggestion that deflazacort may be less prone to cause hyperglycaemia than prednisone must be questioned due to the probably inadequate correction for glucocorticoid potency.[47]

Data from the four extensively reviewed trials on low-dose GC in RA is quite reassuring in this respect: no cases of new-onset diabetes were observed in either of the studies. The Utrecht trial found the least favourable results:[4] a significant increase in mean fasting glucose was seen in the prednisone group (from 5.1 (0.6) at baseline to 5.9 (1.9) mmol/l at 2 years, p= 0.01). However, even in this study, hyperglycemia, as defined by the World Health Organization, developed in only 2 patients in the prednisone group (n=40) and 1 in the placebo group (n=41), see hyperlink 1.

There are no preventive measures apart from the use of lower doses of GC. Alternate–day therapy is associated with alternate-day hyperglycaemia.[48]

In patients with insulin-dependent diabetes exposed to very high doses of GC after kidney transplantation, an insulin dose 58% higher than in those not receiving GC was necessary.[49,50] We could find no studies on the specific effects of low-dose GC in diabetic patients. A relevant and detailed discussion of glucose control under GC treatment has been published.[42]

Fat redistribution and body weight

One of the most notable effects of chronic endogenous and exogenous GC excess is the redistribution of body fat. Centripetal fat accumulation with sparing of the extremities is a characteristic feature of patients exposed to long-term high GC dose. It is seen even with low-dose GC. Potential mechanisms include hyperinsulinemia, changes in expression and activity of adipocyte-derived hormones and cytokines, such as leptin and TNF-α, increased food intake (GC increase appetite) and muscle atrophy.[51-55]

Our own review of toxicity data from the four RA prospective trials shows that low-dose prednisone is associated with an increase of mean body weight over two years, in the range of 4 to 8%. In two of these trials, this weight gain was significantly higher than in the placebo group[3,4] These observations were confirmed in the COBRA trial but the differences were nullified after prednisone was stopped. However, also patients in the control groups gained weight (hyperlink 1 & 2).

Suppression of sex hormones secretion

GC in high doses decrease gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus, decrease basal and GnRH-stimulated LH secretion from the pituitary

and decrease the responsiveness of gonadal cells to LH, leading to lower levels of estrogens[56] and testosterone.[57,58] This latter effect predominates in males.[59] These suppressing effects can contribute to steroid-induced osteoporosis. Despite these observations, it has been suggested that glucocorticoid therapy in rheumatic diseases does not cause a clinically relevant adverse effect on fertility,[60] and decreased libido has not been reported as a common complaint in patients exposed to low-dose GC. In the four extensively reviewed trials on low-dose GC in RA, decreased libido was not reported spontaneously.

Cardiovascular adverse-effects

Dyslipidemia, atherosclerosis and cardiovascular disease

GC treatment is considered to be a risk factor for dyslipidemia and atherosclerosis.[61-64] Several studies in SLE patients suggest that GC therapy is associated with hypercholesterolemia, in a dose-dependent way: significant changes were seen only at prednisone doses higher than 10 mg/day.[65-67] Beyond induction of dyslipidemia, the role of GC in actual atherosclerosis is controversial. Longer steroid use is significantly associated with coronary artery disease in SLE patients.[68-70] Also a study in RA patients suggested that GC treatment early in the disease course increased risk for coronary artery disease.[71] On the other hand, in a study using an animal model of atherosclerosis,[72] although administration of dexamethasone induced hyperlipidemia, it also reduced aortic plaque formation, an effect attributed to inhibition of infiltration of inflammatory and foam cells in the plaques. The recognition of an association between elevated C-reactive protein and accelerated coronary artery disease offers a theoretical basis for glucocorticoid benefit on atherosclerotic disease in the context of inflammatory diseases.[73] Furthermore, recent data from cohorts show that RA disease activity unfavourably alters the blood lipid profile, and treatment (including GC treatment) can reverse these changes.[74] In the four extensively reviewed trials on low-dose GC treatment in RA, lipids were not routinely assessed.

Recently, a record linkage database study on 68781 GC-users (of whom 1115 patients with RA) and 82202 nonusers was published.[75] The incidence of all cardiovascular diseases, including myocardial infarction, heart failure and cerebrovascular disease was not increased in patients using < 7.5 mg prednisolone on a chronic basis. However, it was increased in patients using dosages ≥ 7.5 mg daily: relative risk adjusted for all known risk factors 2.6, 95% confidence interval 2.2 to 3. In the four extensively reviewed trials on low-dose GC treatment in RA and in the COBRA trial, no excess cardiovascular events were reported, but the trial duration of 2 years was relatively short for development of these complications.

In summary, evidence doesn't support a significant role of low-dose GC treatment to the development of cardiovascular disease in RA, in contrast to higher dosages. In patients on low-dose GC, the disease itself seems to be a greater risk factor.

Water and electrolyte balance, oedema, renal and heart function

Hypernatremia, hypokalemia and sodium and water retention are mineralocorticoid effects, produced by endogenous GC at supraphysiologic concentrations.[76] These effects may lead to oedema and contribute to hypertension and heart failure in patients with Cushing's disease. However, synthetic GC (prednisone, prednisolone, methylprednisolone, dexamethasone) have little mineralocorticoid effects, and their administration increases glomerular filtration rate and induces kaliuresis and natriuresis without any change in plasma volume.[77-86] A small number of trials have evaluated

chronic GC administration in moderate to high doses in patients with heart failure, and no significant detrimental effect on heart function emerged from these studies.[87,88] In the four extensively reviewed trials on low-dose GC treatment in RA as well as in the COBRA trial, no cardiac insufficiency attributable to GC occurred.

Hypertension

Induction of hypertension is a well demonstrated adverse effect of GC, observed in about 20% of patients exposed to exogenous GC.[89] The mechanisms involved have not been fully elucidated.[90] A retrospective study of 195 patients with RA or asthma undergoing glucocorticoid therapy with less than 20 mg/day of prednisone for longer than a year,[91] did not show any correlation between dose or duration of GC treatment and rise in blood pressure.

Toxicity data from the four extensively reviewed trials on low-dose GC in RA is very reassuring in respect to blood pressure: there were no significant effects of prednisone upon blood pressure in any of the trials. During the first phase of the COBRA trial, while high to intermediate doses of GC were used, the mean blood pressure was at some points in time higher in the prednisone than in the placebo group. Note that patients with severe hypertension were excluded from most of these trials (hyperlink 1 & 2).

These results suggest that glucocorticoid-induced hypertension is dose-related and is less likely with medium or low-dose therapy. Individual variation in susceptibility and other factors, such as the level of starting blood pressure, diet salt, functional renal mass, associated diseases and drug therapy may play a role in the development of glucocorticoid-induced hypertension.[89] Some authors suggest that the use of alternate-day regimens may reduce the tendency towards blood pressure increase,[92] but evidence for this is weak.

Other cardiac adverse-effects

Incidences of arrhythmia [93] and sudden death are very rare and mostly limited to patients receiving high-dose pulse GC.[94,95] In the four extensively reviewed trials on low-dose GC treatment in RA and in the COBRA trial, these events were not reported.

Dermatological adverse-effects

Clinically relevant adverse-effects on the skin include iatrogenic Cushing's syndrome, catabolic effects (cutaneous atrophy, purpura, striae, easy bruisability and impaired wound healing), steroid acne and hair effects.[96] Cushingoid phenotype is observed in over 5% of the patients exposed to $\geq$ 5 mg prednisone equivalent for $\geq$ 1 year.[97-99] Incidence of iatrogenic Cushing's syndrome is dose-dependent and in general becomes evident after at least one month of glucocorticoid therapy.[96] Some authors suggest that alternate-day administration decreases the development of cushingoid features,[100] but this has not been clearly established.

Catabolic effects on the skin may appear during local and systemic GC therapy. Cutaneous atrophy mainly result from the effect of GC on keratinocytes and fibroblasts. Decreased vascular structural integrity is probably a key determinant of purpura and easy bruisability in GC treated patients.[101] These effects were reported to affect over 5% of those exposed to $\geq$ 5 mg prednisone equivalent for $\geq$ 1 year.[97,102,103] Wound healing impairment seems uncommon at low-dose, but there are no exact data on prevalence. There is no data on incidence of steroid acne and hair effects like hirsutism and hair loss, but they are more frequent with long-term treatment with moderate to high doses of GC, as after organ transplantation.[96] These effects of GC may sometimes be

difficult to separate from those of the disease itself (e.g. hair loss in SLE) and other medications.
Most of the cutaneous adverse-effects of GC are not serious for the doctor, but they may represent a very significant cosmetic problem for the patient. Available data suggest these effects are relatively uncommon and of minor clinical concern with low-dose GC treatment, although data on incidence is scarce. There is no strong evidence to support the claim that use of the lowest possible dose and alternate-day therapy may fully prevent these adverse-effects to occur. In the four extensively reviewed trials on low-dose GC treatment in RA and in the COBRA study, serious cutaneous adverse-effects were not reported, but trial duration was relatively short for development of these complications.

Ophthalmologic adverse effects

Cataract
Long-term use of systemic GC may induce formation of posterior sub-capsular cataract, characterized by disruption of the ordered maturation of the lens fibres, which then accumulate on the front surface of the posterior lens capsule. Cortical cataracts have also been attributed to GC.[104]
Reports on the frequency of cataract with long-term low dose systemic GC therapy are scarce. In a group of RA patients treated with 5 to 15 mg/day of prednisone, mean 6 (SD 3) mg for a mean of 6 (SD 5) years, 15% were found to have cataracts, compared with 4.5% of matched RA controls not using prednisone.[14] There is no evidence that alternate-day therapy reduces the risk.[105] Cataract formation is considered to be irreversible. We could find no evidence regarding the possibility of halting progression with dose reduction or treatment interruption. More careful prospective assessment of cataract formation among GC-users is needed to definitively address this question. In the four extensively reviewed trials on low-dose GC treatment in RA and in the COBRA study, excess cataracts were not reported, but trial duration was probably too short for development of this complication and only two of the four extensively reviewed trials on low-dose GC treatment in RA included a regular ophthalmologic check in a significant number of patients.

Glaucoma
Systemic GC increase the risk of glaucoma and may result in visual field loss or even blindness. In the general population, 18 to 36% of those exposed to GC experience an increase in intraocular pressure.[106] Open-angle glaucoma was found in 6 patients out of 32 rheumatic patients exposed to ≥7.5 mg of prednisone equivalent for more than a year (19%) and in 1 out of 38 treated with <7.5 mg of prednisone equivalent (2.6% - Tryc A, Bartholome,B, Buttgereit F, et al., unpublished data).
However, the occurrence and magnitude of elevation of intraocular pressure with GC administration is highly variable between individuals.[107]. High frequency of this adverse-effect on GC tends to occur in families, suggesting a genetic basis.[108] Patients with pre-existing glaucoma are especially sensitive: 46-92% of patients with open-angle and 65% of those with closed-angle glaucoma will have this condition aggravated upon exposure to GC.[106,109] Patients with diabetes mellitus, high myopia and relatives of those with open-angle glaucoma are reported to be more vulnerable to GC-induced glaucoma[106]. Elevation of intraocular pressure with exogenous GC is generally reversible upon cessation, although it may take several weeks. Medications that lower intraocular pressure may control even a significant pressure increase induced by

concomitant GC.[110] As glaucoma often is asymptomatic and can lead to severe loss of sight, regular eye pressure checks seem thus recommendable for patients on high dose long-term systemic GC treatment, especially for those with associated risk factors for glaucoma. For patients on low-dose GC-therapy and no additional risk factors for glaucoma, it is generally stated that routine checks seem not to be indicated. Only two of the four extensively reviewed trials on low-dose GC treatment in RA included a regular ophthalmologic check in a significant number of patients. However, these checks suggest an increased risk of glaucoma with prednisone (hyperlink 1).

Gastrointestinal adverse-effects

Peptic ulcer disease

The association between GC use and the risk of peptic ulcer disease has been subject of extensive debate and contradictory evidence.[111-113] The influence of the underlying disease on the risk of peptic ulceration is difficult to isolate. Piper et al performed a nested-control study including 1415 patients admitted to the hospital for gastroduodenal ulcer or haemorrhage and 7063 randomly selected controls from Medicaid.[114] The overall estimated relative risk for peptic ulcer disease amongst current GC users was 2.0 (95% CI: 1.3 – 3.0). However, this increased risk was nearly completely due to co-therapy with NSAIDs: the risk for patients co-medicated with NSAIDs was 4.4 (95% CI: 2.0 – 9.7), but for those receiving only GC there was no significant increase in risk: 1.1 (95% CI: 0.5 – 2.1). In large scale studies based on the UK General Practice Research Database,[115] the relative risk of upper G-I complications was 1.8 (95% CI, 1.3–2.4) for users of GC compared to non-users. The risk tended to be greater for higher GC doses but this trend was not statistically significant. The risk was shown to be more than 12 times higher for concomitant users of both GC and NSAIDs, compared with non-users of either drug. Data from the four RA prospective trials and the COBRA study shows no increased incidence of upper GI ulcers and bleeds, but these events are relatively uncommon and may not be detected in these clinical trials with a relatively low number of participating patients (hyperlink 1). In patients treated with GC without concomitant use of NSAIDs there thus seems to be no indication for gastroprotective agents if there are no (other) risk factors for peptic complications.

Pancreatitis

Although GC are usually listed as one of the many potential causes of pancreatitis, evidence for such an association is weak and difficult to separate from the influence of the underlying disease, such as SLE or vasculitis. Experimental and post-mortem studies suggest that GC use is associated with increased incidence of pancreatitis. In one post-mortem study, acute pancreatitis or fat necrosis was observed in 29% of those treated with ACTH or GC vs 4% in the controls.[116] However, none of these patients had been diagnosed with pancreatitis *premortem*, suggesting that clinically relevant pancreatitis due to GC is rare. Controlled studies showed that GC treatment does not cause an increased incidence of pancreatitis in SLE patients.[117] In the four extensively reviewed trials on low-dose GC treatment in RA and in the COBRA study, no case of pancreatitis was reported.

Infectious adverse-effects

The use of GC is associated with increased susceptibility to various viral, bacterial, fungal and parasitic infections. The mechanisms underlying this effect are manifold and not completely understood.[118] Most of these mechanisms, such as the decrease in

function of monocytes, subside rapidly with treatment interruption, an observation that may explain the lower infectious risk with the use of short-acting GC and alternate day therapy.[119,120] The risk of infection increases with dose and duration of treatment,[121] and tends to remain low in patients exposed to low-doses, even with high cumulative dosages.[122] In a meta-analysis of 71 trials involving over 2000 patients with different diseases and different dosages of GC, a relative risk of infection was found of 2.0.[123] Five of these 71 trials involved patients with rheumatic diseases and showed no increased relative risk. In two studies specifically on RA the incidence of serious infections was found to be similar to that of placebo or only slightly increased.[4,14] SLE is associated with increased risk of opportunistic infections, exacerbated by therapy with GC.[124,125] Of the intensively reviewed four studies of low-dose GC therapy in RA, both in the Utrecht and the Woseract trials, prednisone in up to 10mg/day was not associated with increased incidence of any kind of infections over the two years of the trials.[4,5]
In patients treated with GC, physicians should anticipate the risk of infections with both usual and unusual organisms, realizing that GC may blunt the classic clinical features and delay the diagnosis. Under special clinical circumstances and in severely immuno-compromised patients it may be wise to screen for latent infections, such as tuberculosis, or institute prophylactic chemotherapy.[122] Pneumocystis carinii infections deserve special attention, as doses as low as 16 mg per day of prednisone for eight weeks have been associated with increased risk in one series.[126]

Psychologic and behavioural disturbances

Steroid psychosis
Psychosis is characterized by hallucinations, delusions or both. Estimates of the incidence of steroid psychosis vary greatly in literature (0 - 60%), due to differences in study populations and methodology of assessing this adverse-event. Following an authoritative review, the estimate of incidence of 5 to 6% has become consensual in the literature.[127] However, most cases are associated with high doses of GC and an influence of the underlying disease, such as SLE, is frequently difficult to exclude. A landmark study in this area is the Boston Cooperative Drug Surveillance Program.[128] The incidence of steroid psychosis in 718 prednisone treated patients was 1.3% at 40 mg daily, 4-5% at 41 to 80 mg and over 18% with higher doses. Several studies regarding doses of 20mg or less did not find cases of psychosis.[129] Nor in the four extensively reviewed trials on low-dose GC treatment in RA, nor in the COBRA-study, this adverse-event was reported.
Thus the clinician should be aware of this adverse-effect and its clinical features,[130,131] but overt psychosis is extremely rare with the low and medium dose regimes usually employed in rheumatology.

Minor mood disturbances
GC treatment has been associated with a variety of low-grade disturbances such as depressed or elated mood (euphoria), irritability or emotional lability, anxiety and insomnia, memory and cognition impairments. The exact incidence of such symptoms in rheumatic patients exposed to common doses of GC cannot be drawn from the literature. Most studies relate to doses of 80 to 160mg of prednisone equivalent per day, far exceeding common long-term regimes in rheumatology.[132] Evidence regarding minor effects is scarce but doses of less than 20 to 25 mg prednisone equivalent are associated with few or no significant disturbances.[133,134] However, individual susceptibility is highly variable and there are a few published cases where relationship

between low-dose GC and even topical steroids and psychotic episodes seems hard to doubt. In the four extensively reviewed trials on low-dose GC treatment in RA, nor in the COBRA-study, these adverse-event were reported, but they were not systematically assessed either.

Drug Interactions

Significant interactions between GC and other prescription therapies have been well documented. Drugs that *reduce* the systemic GC concentration may diminish clinical efficacy. They include large doses of aluminum/magnesium hydroxide, which decrease prednisone bioavailability by 30 to 40 percent,[135,136] and most anticonvulsants (eg, phenobarbital, phenytoin), which enhance the metabolism of GC.[137-142] Rifampin accelerates the metabolism of synthetic steroids as may St. John's wort.[143] Rifampin-induced non-responsiveness to prednisone of inflammatory diseases has been described and rifampin-induced adrenal crisis in patients on GC replacement therapy has been documented.[144-147]

Drugs that *raise* the systemic GC concentration include some oral contraceptives,[148-151] antibiotics (erythromycin and troleandomycin).[152-154] Antifungal agents, particularly ketoconazole decrease GC metabolising enzymes.[155,156] Some data suggests that several NSAIDs, including indomethacin and naproxen, increase GC concentrations.[157] The other way round, GC may affect serum concentration, efficacy or toxicity of other drugs, such as warfarin and salicylates.[158,159] In addition, when used concomitantly with traditional NSAIDs, GC cause an increased risk of upper gastrointestinal adverse events, particularly in patients with RA, see above.[115,160]

Nor the four extensively reviewed trials on low-dose GC treatment in RA, nor in the COBRA-study, were adequate to study these interactions.

Conclusions and research agenda

After a careful literature review of the adverse-effects of low-dose GC, extensive review of adverse-effects of four trials on low-dose GC treatment in RA and the COBRA study, and extensive group discussions, the authors' main conclusion is that definitive associations of low-dose GC with many adverse-effects remain elusive. The overall fear of GC toxicity in RA, as quoted in textbooks and review articles, is probably overestimated based on extrapolation from observations with higher dose therapy. The balance of risks and benefits of low dose therapy clearly differs from that of medium and high dose therapy, of which the mechanisms of action of GC may be different.[161]This may explain why GC are used in practice in more patients than the more pessimist recommendations suggest. Physicians, and probably patients, seem to value the benefit/risk ratio of low-dose GC. There is surprisingly weak evidence on which to support clear recommendations about toxicity of low-dose GC. The literature and the recent trial results suggest that routine toxicity monitoring for patients on low-dose GC is not currently justifiable or cost effective based on existing evidence. However, patients with additional risk factors (e.g. osteoporosis, obesity, hypertension, family history of diabetes or glaucoma) merit more careful observation (Table 2).

Table 2. Glucocorticoid related adverse-effects other than osteoporosis that may justify clinical control.

- Cushingoid symptoms
- Adrenal crisis on glucocorticoid withdrawal
- Growth retardation in children
- New onset of diabetes mellitus in subjects at risk for developing DM

- Worsening of glycemia control in patients with diabetes mellitus
- Cataracts and glaucoma
- Peptic ulcer (if associated with NSAIDs)
- Hypertension

GC will likely retain an enormous therapeutic value in treatment of a large variety of rheumatic conditions for many years to come, especially since it becomes increasingly clear that they have disease modifying potential. The data reported in this paper of trials not primarily designed for assessment of adverse effects and of observational studies with possible bias, especially confounding by indication, do not represent the highest level of evidence. So safety of low-dose GC also needs to undergo serious and systematic re-evaluation with properly designed and dedicated studies of adequate size, duration, and utilizing state-of-the-art endpoints. Guidelines for such studies would enhance comprehensiveness and comparability. We believe the areas listed in Table 2 should be further explored when new studies of low dose GC are to be undertaken, and physicians might wish to consider these issues in clinical practice when prescribing GC treatment. Furthermore, subjects participating in randomised clinical trials may not have the same disease characteristics or comorbidities of patients treated in the community, thereby limiting the generalizability of findings of this kind of trials.[162] So, simple, pragmatic trials with appropriate patient selection and sufficiently long duration are also needed.

Other areas of research include the best timing of administration, the potential advantages and limitations of alternate-day dosing, identification of risk factors for such adverse-effects as upper G-I complications, glaucoma, cataract, and studies of the individual sensitivity to GC related to underlying mechanisms, such as receptor gene polymorphisms.[163] Elucidation of the biological mechanisms involved in these effects will open new opportunities for prevention and treatment. Research on the potential separation of wanted from unwanted GC effects using newly designed GC-type medicine provides good reason for hope that an even better safety/efficacy ratio can be achieved in the future.[164]

Competing interest.

None of the authors recognize any competing interest relevant to this paper.

References

1. Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. N Engl J Med 1995; 333:142-6.

2. Hickling P, Jacoby RK, Kirwan JR. Joint destruction after glucocorticoids are withdrawn in early rheumatoid arthritis. Arthritis and Rheumatism Council Low Dose Glucocorticoid Study Group. Br J Rheumatol 1998; 37:930-6.

3. Rau R, Wassenberg S, Zeidler H. Low dose prednisolone therapy (LDPT) retards radiographically detectable destruction in early rheumatoid arthritis--preliminary results of a multicenter, randomized, parallel, double blind study. Z Rheumatol 2000; 59 Suppl 2:II/90-II/96.

4. van Everdingen AA, Jacobs JW, Siewertsz van Reesema DR, Bijlsma JW. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial. Ann Intern Med 2002; 136:1-12.

5. Capell HA, Madhok R, Hunter JA, Porter D, Morrison E, Larkin J, et al. Lack of radiological and clinical benefit over two years of low dose prednisolone for rheumatoid arthritis: results of a randomised controlled trial. Ann Rheum Dis 2004; 63:797-803.

6. Laan RF, van Riel PL, van de Putte LB, van Erning LJ, van't Hof MA, Lemmens JA. Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis. A randomized, controlled study. Ann Intern Med 1993; 119:963-8.

7. de Nijs RN, Jacobs JW, Bijlsma JW, Lems WF, Laan RF, Houben HH, et al. Prevalence of vertebral deformities and symptomatic vertebral fractures in corticosteroid treated patients with rheumatoid arthritis. Rheumatology (Oxford) 2001; 40:1375-83.

8. van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporos Int 2002; 13:777-87.

9. Gluck OS, Murphy WA, Hahn TJ, Hahn B. Bone loss in adults receiving alternate day glucocorticoid therapy. A comparison with daily therapy. Arthritis Rheum 1981; 24:892-8.

10. Ruegsegger P, Medici TC, Anliker M. Corticosteroid-induced bone loss. A longitudinal study of alternate day therapy in patients with bronchial asthma using quantitative computed tomography. Eur J Clin Pharmacol 1983; 25:615-20.

11. Verhoeven AC, Boers M. Limited bone loss due to corticosteroids; a systematic review of prospective studies in rheumatoid arthritis and other diseases. J Rheumatol 1997; 24:1495-503.

12. Lodder MC, Lems WF, Kostense PJ, Verhoeven AC, Dijkmans BA, Boers M. Bone loss due to glucocorticoids: update of a systematic review op prospective studies in rheumatoid arthritis and other diseases. Ann Rheum Dis 2003; 62:94.

13. Bijlsma JWJ. Long-term glucocorticoid treatment of rheumatoid arthritis: risk or benefit? Rheumatology in Europe 1998; 27:67-71.

14. Saag KG, Koehnke R, Caldwell JR, Brasington R, Burmeister LF, Zimmerman B, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. Am J Med 1994; 96:115-23.

15. van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. J Bone Miner Res 2000; 15:993-1000.

16. Reid IR, Heap SW. Determinants of vertebral mineral density in patients receiving long-term glucocorticoid therapy. Arch Intern Med 1990; 150:2545-8.

17. Lems WF, Jahangier ZN, Jacobs JW, Bijlsma JW. Vertebral fractures in patients with rheumatoid arthritis treated with corticosteroids. Clin Exp Rheumatol 1995; 13:293-7.

18. Naganathan V, Jones G, Nash P, Nicholson G, Eisman J, Sambrook PN. Vertebral fracture risk with long-term corticosteroid therapy: prevalence and relation to age, bone density, and corticosteroid use. Arch Intern Med 2000; 160:2917-22.

19. Sambrook P, Lane NE. Corticosteroid osteoporosis. Best Pract Res Clin Rheumatol 2001; 15:401-13.

20. Boers M, Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van Denderen JC, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997; 350:309-18.

21. Dequeker J, Westhovens R, Luyten FP. Rheumatic disorders and glucocorticoid-induced osteoporosis. Front Horm Res 2002; 30:107-20.

22. Yeap SS, Hosking DJ. Management of corticosteroid-induced osteoporosis. Rheumatology (Oxford) 2002; 41:1088-94.

23. Anonymous. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. American College of Rheumatology Ad Hoc Committee on Glucocoritcoid-Induced Osteoporosis. Arthritis Rheum 2001; 44:1496-503.

24. Eastell R, Reid DM, Compston J, Cooper C, Fogelman I, Francis RM, et al. A UK Consensus Group on management of glucocorticoid-induced osteoporosis: an update. J Intern Med 1998; 244:271-92.

25. Anonymous. Guidelines on the prevention and treatment of glucocorticoid induced osteoporosis by the Bone and Tooth Society, National Osteoporosis Society and Royal College of Physicians. www rcplondon ac uk/pubs/books/glucocorticoid/index asp (accessed November, 2004).

26. Ninomija S. An epidemiologic survey of idiopathic avascular necrosis of the femoral head in Japan. Annual Report of Japanese Investigation Committee for Intractable Disease. Osaka: University Publisher, 1984.

27. Zizic TM, Marcoux C, Hungerford DS, Dansereau JV, Stevens MB. Corticosteroid therapy associated with ischemic necrosis of bone in systemic lupus erythematosus. Am J Med 1985; 79:596-604.

28. Gebhard KL, Maibach HI. Relationship between systemic corticosteroids and osteonecrosis. Am J Clin Dermatol 2001; 2:377-88.

29. Vreden SG, Hermus AR, van Liessum PA, Pieters GF, Smals AG, Kloppenborg PW. Aseptic bone necrosis in patients on glucocorticoid replacement therapy. Neth J Med 1991; 39:153-7.

30. Zonana-Nacach A, Barr SG, Magder LS, Petri M. Damage in systemic lupus erythematosus and its association with corticosteroids. Arthritis Rheum 2000; 43:1801-8.

31. Klipple JH. Osteonecrosis. Primer on the Rheumatic Diseases. Arthritis Foundation, 2001: 503-6.

32. Kagen LJ. Steroid Myopathy. In: Lin NA, Paget SA, editors. Principles of corticosteroid therapy. London: Arnold, 2002: 87-90.

33. Danneskiold-Samsoe B, Grimby G. The influence of prednisone on the muscle morphology and muscle enzymes in patients with rheumatoid arthritis. Clin Sci (Lond) 1986; 71:693-701.

34. Moxley RT. Metabolic and endocrine myopathies. In: Walton JN, Karpati G, Jones DH, editors. Disorders of voluntary muscle. Edinburgh: Churchil Livingstone, 1994: 647.

35. Tayek JA, Katz J. Glucose production, recycling, Cori cycle, and gluconeogenesis in humans: relationship to serum cortisol. Am J Physiol 1997; 272:E476-E484.

36. Delaunay F, Khan A, Cintra A, Davani B, Ling ZC, Andersson A, et al. Pancreatic beta cells are important targets for the diabetogenic effects of glucocorticoids. J Clin Invest 1997; 100:2094-8.

37. Lambillotte C, Gilon P, Henquin JC. Direct glucocorticoid inhibition of insulin secretion. An in vitro study of dexamethasone effects in mouse islets. J Clin Invest 1997; 99:414-23.

38. Hosker JP, Burnett MA, Matthews DR, Turner RC. Prednisolone enhances beta-cell function independently of ambient glycemic levels in type II diabetes. Metabolism 1993; 42:1116-20.

39. Kautzky-Willer A, Thomaseth K, Clodi M, Ludvik B, Waldhausl W, Prager R, et al. Beta-cell activity and hepatic insulin extraction following dexamethasone administration in healthy subjects. Metabolism 1996; 45:486-91.

40. Tounian P, Schneiter P, Henry S, Delarue J, Tappy L. Effects of dexamethasone on hepatic glucose production and fructose metabolism in healthy humans. Am J Physiol 1997; 273:E315-E320.

41. Hirsch IB, Paauw DS. Diabetes management in special situations. Endocrinol Metab Clin North Am 1997; 26:631-45.

42. Hoogwerf B, Danese RD. Drug selection and the management of corticosteroid-related diabetes mellitus. Rheum Dis Clin North Am 1999; 25:489-505.

43. Gurwitz JH, Bohn RL, Glynn RJ, Monane M, Mogun H, Avorn J. Glucocorticoids and the risk for initiation of hypoglycemic therapy. Arch Intern Med 1994; 154:97-101.

44. Black DM, Filak AT. Hyperglycemia with non-insulin-dependent diabetes following intraarticular steroid injection. J Fam Pract 1989; 28:462-3.

45. Hricik DE, Bartucci MR, Moir EJ, Mayes JT, Schulak JA. Effects of steroid withdrawal on posttransplant diabetes mellitus in cyclosporine-treated renal transplant recipients. Transplantation 1991; 51:374-7.

46. Liapi C, Chrousos GP. Glucocorticoids. In: Yaffe SJ, Arand JV, editors. Pediatric Pharmacology. Philadelphia: WB Saunders, 1992: 466.

47. Bruno A, Cavallo-Perin P, Cassader M, Pagano G. Deflazacort vs prednisone. Effect on blood glucose control in insulin-treated diabetics. Arch Intern Med 1987; 147:679-80.

48. Greenstone MA, Shaw AB. Alternate day corticosteroid causes alternate day hyperglycaemia. Postgrad Med J 1987; 63:761-4.

49. Barbosa J, Menth L, Eaton J, Sutherland D, Freier EF, Najarian J. Long-term, ambulatory, subcutaneous insulin infusion versus multiple daily injections in brittle diabetic patients. Diabetes Care 1981; 4:269-74.

50. Ekstrand A, Ahonen J, Gronhagen-Riska C, Groop L. Mechanisms of insulin resistance after kidney transplantation. Transplantation 1989; 48:563-8.

51. Licinio J, Mantzoros C, Negrao AB, Cizza G, Wong ML, Bongiorno PB, et al. Human leptin levels are pulsatile and inversely related to pituitary-adrenal function. Nat Med 1997; 3:575-9.

52. Stewart PM, Tomlinson JW. Cortisol, 11 beta-hydroxysteroid dehydrogenase type 1 and central obesity. Trends Endocrinol Metab 2002; 13:94-6.

53. Tomlinson JW, Moore J, Cooper MS, Bujalska I, Shahmanesh M, Burt C, et al. Regulation of expression of 11beta-hydroxysteroid dehydrogenase type 1 in adipose tissue: tissue-specific induction by cytokines. Endocrinology 2001; 142:1982-9.

54. Reilly JJ, Brougham M, Montgomery C, Richardson F, Kelly A, Gibson BE. Effect of glucocorticoid therapy on energy intake in children treated for acute lymphoblastic leukemia. J Clin Endocrinol Metab 2001; 86:3742-5.

55. Tataranni PA, Larson DE, Snitker S, Young JB, Flatt JP, Ravussin E. Effects of glucocorticoids on energy metabolism and food intake in humans. Am J Physiol 1996; 271:E317-E325.

56. Nordin BE, Crilly RG, Marshall DH, Barkworth SA. Oestrogens, the menopause and the adrenopause. J Endocrinol 1981; 89 Suppl:131P-43P.

57. Hampson G, Bhargava N, Cheung J, Vaja S, Seed PT, Fogelman I. Low circulating estradiol and adrenal androgens concentrations in men on glucocorticoids: a potential contributory factor in steroid-induced osteoporosis. Metabolism 2002; 51:1458-62.

58. MacAdams MR, White RH, Chipps BE. Reduction of serum testosterone levels during chronic glucocorticoid therapy. Ann Intern Med 1986; 104:648-51.

59. Cumming DC, Quigley ME, Yen SS. Acute suppression of circulating testosterone levels by cortisol in men. J Clin Endocrinol Metab 1983; 57:671-3.

60. Janssen NM, Genta MS. The effects of immunosuppressive and anti-inflammatory medications on fertility, pregnancy, and lactation. Arch Intern Med 2000; 160:610-9.

61. Becker DM, Chamberlain B, Swank R, Hegewald MG, Girardet R, Baughman KL, et al. Relationship between corticosteroid exposure and plasma lipid levels in heart transplant recipients. Am J Med 1988; 85:632-8.

62. Cattran DC, Steiner G, Wilson DR, Fenton SA. Hyperlipidemia after renal transplantation: natural history and pathophysiology. Ann Intern Med 1979; 91:554-9.

63. Curtis JJ, Galla JH, Woodford SY, Lucas BA, Luke RG. Effect of alternate-day prednisone on plasma lipids in renal transplant recipients. Kidney Int 1982; 22:42-7.

64. el-Shaboury AH, Hayes TM. Hyperlipidaemia in asthmatic patients receiving long-term steroid therapy. Br Med J 1973; 2:85-6.

65. MacGregor AJ, Dhillon VB, Binder A, Forte CA, Knight BC, Betteridge DJ, et al. Fasting lipids and anticardiolipin antibodies as risk factors for vascular disease in systemic lupus erythematosus. Ann Rheum Dis 1992; 51:152-5.

66. Petri M, Spence D, Bone LR, Hochberg MC. Coronary artery disease risk factors in the Johns Hopkins Lupus Cohort: prevalence, recognition by patients, and preventive practices. Medicine (Baltimore) 1992; 71:291-302.

67. Leong KH, Koh ET, Feng PH, Boey ML. Lipid profiles in patients with systemic lupus erythematosus. J Rheumatol 1994; 21:1264-7.

68. Manzi S, Meilahn EN, Rairie JE, Conte CG, Medsger TA, Jr., Jansen-McWilliams L, et al. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. Am J Epidemiol 1997; 145:408-15.

69. Petri M, Perez-Gutthann S, Spence D, Hochberg MC. Risk factors for coronary artery disease in patients with systemic lupus erythematosus. Am J Med 1992; 93:513-9.

70. Manzi S, Selzer F, Sutton-Tyrrell K, Fitzgerald SG, Rairie JE, Tracy RP, et al. Prevalence and risk factors of carotid plaque in women with systemic lupus erythematosus. Arthritis Rheum 1999; 42:51-60.

71. Wallberg-Jonsson S, Johansson H, Ohman ML, Rantapaa-Dahlqvist S. Extent of inflammation predicts cardiovascular disease and overall mortality in seropositive rheumatoid arthritis. A retrospective cohort study from disease onset. J Rheumatol 1999; 26:2562-71.

72. Asai K, Funaki C, Hayashi T, Yamada K, Naito M, Kuzuya M, et al. Dexamethasone-induced suppression of aortic atherosclerosis in cholesterol-fed rabbits. Possible mechanisms. Arterioscler Thromb 1993; 13:892-9.

73. Munford RS. Statins and the acute-phase response. N Engl J Med 2001; 344:2016-8.

74. Boers M, Nurmohamed MT, Doelman CJ, Lard LR, Verhoeven AC, Voskuyl AE, et al. Influence of glucocorticoids and disease activity on total and high density lipoprotein cholesterol in patients with rheumatoid arthritis. Ann Rheum Dis 2003; 62:842-5.

75. Wei L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. Ann Intern Med 2004; 141:764-70.

76. Connell JM, Whitworth JA, Davies DL, Lever AF, Richards AM, Fraser R. Effects of ACTH and cortisol administration on blood pressure, electrolyte metabolism, atrial natriuretic peptide and renal function in normal man. J Hypertens 1987; 5:425-33.

77. Bia JM, Tyler K, DeFronzo RA. The effect of dexamethasone on renal electrolyte excretion in the adrenalectomized rat. Endocrinology 1982; 111:882-8.

78. Campen TJ, Vaughn DA, Fanestil DD. Mineralo- and glucocorticoid effects on renal excretion of electrolytes. Pflugers Arch 1983; 399:93-101.

79. Hall JE, Morse CL, Smith MJ, Jr., Young DB, Guyton AC. Control of arterial pressure and renal function during glucocorticoid excess in dogs. Hypertension 1980; 2:139-48.

80. Kohlmann O, Jr., Ribeiro AB, Marson O, Saragoca MA, Ramos OL. Methylprednisolone-induced hypertension. Role for the autonomic and renin angiotensin systems. Hypertension 1981; 3:II-11.

81. Krakoff LR, Selvadurai R, Sutter E. Effect of methylprednisolone upon arterial pressure and the renin angiotensin system in the rat. Am J Physiol 1975; 228:613-7.

82. Kurokawa K, Fukagawa M, Hayashi M, et al. Renal receptors and cellular mechanisms of hormone action in the kidney. In: Seldin DW, Giebisch G, editors. The Kidney. New York: Raven Press, 1992: 1339-72.

83. Nakamoto H, Suzuki H, Kageyama Y, Ohishi A, Murakami M, Naitoh M, et al. Characterization of alterations of hemodynamics and neuroendocrine hormones in dexamethasone induced hypertension in dogs. Clin Exp Hypertens A 1991; 13:587-606.

84. Nelson MA, Coghlan JP, Denton DA, Mills EH, Spence CD, Scoggins BA. Metabolic and blood pressure effects of 6 alpha-methylprednisolone in the conscious sheep. Clin Exp Hypertens A 1984; 6:1067-75.

85. Okuno T, Suzuki H, Saruta T. Dexamethasone hypertension in rats. Clin Exp Hypertens 1981; 3:1075-86.

86. Whitworth JA, Gordon D, Andrews J, Scoggins BA. The hypertensive effect of synthetic glucocorticoids in man: role of sodium and volume. J Hypertens 1989; 7:537-49.

87. Latham RD, Mulrow JP, Virmani R, Robinowitz M, Moody JM. Recently diagnosed idiopathic dilated cardiomyopathy: incidence of myocarditis and efficacy of prednisone therapy. Am Heart J 1989; 117:876-82.

88. Mason JW, O'Connell JB, Herskowitz A, Rose NR, McManus BM, Billingham ME, et al. A clinical trial of immunosuppressive therapy for myocarditis. The Myocarditis Treatment Trial Investigators. N Engl J Med 1995; 333:269-75.

89. Whitworth JA. Mechanisms of glucocorticoid-induced hypertension. Kidney Int 1987; 31:1213-24.

90. Sholter DE, Armstrong PW. Adverse effects of corticosteroids on the cardiovascular system. Can J Cardiol 2000; 16:505-11.

91. Jackson SH, Beevers DG, Myers K. Does long-term low-dose corticosteroid therapy cause hypertension? Clin Sci (Lond) 1981; 61 Suppl 7:381s-3s.

92. McHugh MI, Tanboga H, Wilkinson R. Alternate day steroids and blood pressure control after renal transplantation. Proc Eur Dial Transplant Assoc 1980; 17:496-501.

93. Singh RG, Kassir M, Roistacher N, Lerman BB, Kligfield P. Acceleration of atrioventricular conduction during corticosteroid therapy. Am Heart J 1993; 125:1432-4.

94. Smith RS, Warren DJ. Effects of high-dose intravenous methylprednisolone on circulation in humans. Transplantation 1983; 35:349-51.

95. Thompson JF, Chalmers DH, Wood RF, Kirkham SR, Morris PJ. Sudden death following high-dose intravenous methylprednisolone. Transplantation 1983; 36:594-6.

96. Wolverton SE. Corticosteroids and the integument. In: Lin AN, Paget SA, editors. Principles of Corticosteroid Therapy. London: Arnold, 2002: 166-72.

97. Covar RA, Leung DY, McCormick D, Steelman J, Zeitler P, Spahn JD. Risk factors associated with glucocorticoid-induced adverse effects in children with severe asthma. J Allergy Clin Immunol 2000; 106:651-9.

98. Marcocci C, Bartalena L, Tanda ML, Manetti L, Dell'Unto E, Rocchi R, et al. Comparison of the effectiveness and tolerability of intravenous or oral glucocorticoids associated with orbital radiotherapy in the management of severe Graves' ophthalmopathy: results of a prospective, single-blind, randomized study. J Clin Endocrinol Metab 2001; 86:3562-7.

99. Tornatore KM, Biocevich DM, Reed K, Tousley K, Singh JP, Venuto RC. Methylprednisolone pharmacokinetics, cortisol response, and adverse effects in black and white renal transplant recipients. Transplantation 1995; 59:729-36.

100. Pedrosa MC, Rohrer RM, Kaplan MM. Alternate-day prednisone in the maintenance immunosuppressive therapy after orthotopic liver transplantation. Clin Transplant 1995; 9:322-5.

101. Davis GF. Adverse effects of corticosteroids: II. Systemic. Clin Dermatol 1986; 4:161-9.

102. Caldwell JR, Furst DE. The efficacy and safety of low-dose corticosteroids for rheumatoid arthritis. Semin Arthritis Rheum 1991; 21:1-11.

103. Hatz HJ, Helmke K. [Polymyalgia rheumatica and giant cell arteritis; diagnosis and side effects of low-dose long-term glucocorticoid therapy]. Z Rheumatol 1992; 51:213-21.

104. Klein R, Klein BE, Lee KE, Cruickshanks KJ, Chappell RJ. Changes in visual acuity in a population over a 10-year period : The Beaver Dam Eye Study. Ophthalmology 2001; 108:1757-66.

105. Rooklin AR, Lampert SI, Jaeger EA, McGeady SJ, Mansmann HC, Jr. Posterior subcapsular cataracts in steroid-requiring asthmatic children. J Allergy Clin Immunol 1979; 63:383-6.

106. Tripathi RC, Parapuram SK, Tripathi BJ, Zhong Y, Chalam KV. Corticosteroids and glaucoma risk. Drugs Aging 1999; 15:439-50.

107. Klemetti A. The dexamethasone provocative test: a predictive tool for glaucoma? Acta Ophthalmol (Copenh) 1990; 68:29-33.

108. Stone EM, Fingert JH, Alward WL, Nguyen TD, Polansky JR, Sunden SL, et al. Identification of a gene that causes primary open angle glaucoma. Science 1997; 275:668-70.

109. Akingbehin AO. Corticosteroid-induced ocular hypertension. I. Prevalence in closed-angle glaucoma. Br J Ophthalmol 1982; 66:536-40.

110. Brodie S. Corticosteroids and the eye. In: Lin AN, Paget SA, editors. Principles of corticosteroid therapy. London: Arnold, 2002: 131-4.

111. Conn HO, Blitzer BL. Nonassociation of adrenocorticosteroid therapy and peptic ulcer. N Engl J Med 1976; 294:473-9.

112. Conn HO, Poynard T. Corticosteroids and peptic ulcer: meta-analysis of adverse events during steroid therapy. J Intern Med 1994; 236:619-32.

113. Messer J, Reitman D, Sacks HS, Smith H, Jr., Chalmers TC. Association of adrenocorticosteroid therapy and peptic-ulcer disease. N Engl J Med 1983; 309:21-4.

114. Piper JM, Ray WA, Daugherty JR, Griffin MR. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. Ann Intern Med 1991; 114:735-40.

115. Garcia Rodriguez LA, Hernandez-Diaz S. The risk of upper gastrointestinal complications associated with nonsteroidal anti-inflammatory drugs, glucocorticoids, acetaminophen, and combinations of these agents. Arthritis Res 2001; 3:98-101.

116. CARONE FA, LIEBOW AA. Acute pancreatic lesions in patients treated with ACTH and adrenal corticoids. N Engl J Med 1957; 257:690-7.

117. Saab S, Corr MP, Weisman MH. Corticosteroids and systemic lupus erythematosus pancreatitis: a case series. J Rheumatol 1998; 25:801-6.

118. Baxter JD. Advances in glucocorticoid therapy. In: Schrier RW BJDVFAe, editor. St Louis: Mosby, 2000: 317-49.

119. Baxter JD. Minimizing the side effects of glucocorticoid therapy. Adv Intern Med 1990; 35:173-93.

120. Dale DC, Fauci AS, Wolff SM. Alternate-day prednisone. Leukocyte kinetics and susceptibility to infections. N Engl J Med 1974; 291:1154-8.

121. Dale DC, Petersdorf RG. Corticosteroids and infectious diseases. Med Clin North Am 1973; 57:1277-87.

122. Stracher AR, Soave R. Infectious complications of corticosteroid therapy. In: Linn AN, Paget SA, editors. Principles of corticosteroid therapy. London: 2002: 419-30.

123. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. Rev Infect Dis 1989; 11:954-63.

124. Godeau B, Coutant-Perronne V, Le Thi HD, Guillevin L, Magadur G, De BM, et al. Pneumocystis carinii pneumonia in the course of connective tissue disease: report of 34 cases. J Rheumatol 1994; 21:246-51.

125. Hellmann DB, Petri M, Whiting-O'Keefe Q. Fatal infections in systemic lupus erythematosus: the role of opportunistic organisms. Medicine (Baltimore) 1987; 66:341-8.

126. Yale SH, Limper AH. Pneumocystis carinii pneumonia in patients without acquired immunodeficiency syndrome: associated illness and prior corticosteroid therapy. Mayo Clin Proc 1996; 71:5-13.

127. Lewis DA, Smith RE. Steroid-induced psychiatric syndromes. A report of 14 cases and a review of the literature. J Affect Disord 1983; 5:319-32.

128. Gourley MF, Austin HA, III, Scott D, Yarboro CH, Vaughan EM, Muir J, et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. Ann Intern Med 1996; 125:549-57.

129. Smyllie HC, Connolly CK. Incidence of serious complications of corticosteroid therapy in respiratory disease. A retrospective survey of patients in the Brompton hospital. Thorax 1968; 23:571-81.

130. Demopoulos A, Apatoff BR. Corticosteroids and the nervous system. In: Lin NA, Paget SA, editors. Principles of corticosteroid therapy. London: Arnold, 2002: 150-65.

131. Patten SB, Neutel CI. Corticosteroid-induced adverse psychiatric effects: incidence, diagnosis and management. Drug Saf 2000; 22:111-22.

132. Naber D, Sand P, Heigl B. Psychopathological and neuropsychological effects of 8-days' corticosteroid treatment. A prospective study. Psychoneuroendocrinology 1996; 21:25-31.

133. Olsen EA, Carson SC, Turney EA. Systemic steroids with or without 2% topical minoxidil in the treatment of alopecia areata. Arch Dermatol 1992; 128:1467-73.

134. Reckart MD, Eisendrath SJ. Exogenous corticosteroid effects on mood and cognition: case presentations. Int J Psychosom 1990; 37:57-61.

135. Tanner AR, Caffin JA, Halliday JW, Powell LW. Concurrent administration of antacids and prednisone: effect on serum levels of prednisolone. Br J Clin Pharmacol 1979; 7:397-400.

136. Uribe M, Casian C, Rojas S, Sierra JG, Go VL. Decreased bioavailability of prednisone due to antacids in patients with chronic active liver disease and in healthy volunteers. Gastroenterology 1981; 80:661-5.

137. Brooks SM, Werk EE, Ackerman SJ, Sullivan I, Thrasher K. Adverse effects of phenobarbital on corticosteroid metabolism in patients with bronchial asthma. N Engl J Med 1972; 286:1125-8.

138. Evans PJ, Walker RF, Peters JR, Dyas J, Riad-Fahmy D, Thomas JP, et al. Anticonvulsant therapy and cortisol elimination. Br J Clin Pharmacol 1985; 20:129-32.

139. Frey BM, Frey FJ. Phenytoin modulates the pharmacokinetics of prednisolone and the pharmacodynamics of prednisolone as assessed by the inhibition of the mixed lymphocyte reaction in humans. Eur J Clin Invest 1984; 14:1-6.

140. Frey FJ, Frey BM. Urinary 6 beta-hydroxyprednisolone excretion indicates enhanced prednisolone catabolism. J Lab Clin Med 1983; 101:593-604.

141. Petereit LB, Meikle AW. Effectiveness of prednisolone during phenytoin therapy. Clin Pharmacol Ther 1977; 22:912-6.

142. Stjernholm MR, Katz FH. Effects of diphenylhydantoin, phenobarbital, and diazepam on the metabolism of methylprednisolone and its sodium succinate. J Clin Endocrinol Metab 1975; 41:887-93.

143. Edwards OM, Courtenay-Evans RJ, Galley JM, Hunter J, Tait AD. Changes in cortisol metabolism following rifampicin therapy. Lancet 1974; 2:548-51.

144. Carrie F, Roblot P, Bouquet S, Delon A, Roblot F, Becq-Giraudon B. Rifampin-induced nonresponsiveness of giant cell arteritis to prednisone treatment. Arch Intern Med 1994; 154:1521-4.

145. Kawai S, Ichikawa Y, Homma M. [Rifampicin-induced resistance to prednisolone treatment in collagen disease--a pharmacokinetic study]. Ryumachi 1984; 24:32-7.

146. McAllister WA, Thompson PJ, Al-Habet SM, Rogers HJ. Rifampicin reduces effectiveness and bioavailability of prednisolone. Br Med J (Clin Res Ed) 1983; 286:923-5.

147. Kyriazopoulou V, Parparousi O, Vagenakis AG. Rifampicin-induced adrenal crisis in addisonian patients receiving corticosteroid replacement therapy. J Clin Endocrinol Metab 1984; 59:1204-6.

148. Boekenoogen SJ, Szefler SJ, Jusko WJ. Prednisolone disposition and protein binding in oral contraceptive users. J Clin Endocrinol Metab 1983; 56:702-9.

149. Frey BM, Schaad HJ, Frey FJ. Pharmacokinetic interaction of contraceptive steroids with prednisone and prednisolone. Eur J Clin Pharmacol 1984; 26:505-11.

150. Gustavson LE, Legler UF, Benet LZ. Impairment of prednisolone disposition in women taking oral contraceptives or conjugated estrogens. J Clin Endocrinol Metab 1986; 62:234-7.

151. Olivesi A. Modified elimination of prednisolone in epileptic patients on carbamazepine monotherapy, and in women using low-dose oral contraceptives. Biomed Pharmacother 1986; 40:301-8.

152. LaForce CF, Szefler SJ, Miller MF, Ebling W, Brenner M. Inhibition of methylprednisolone elimination in the presence of erythromycin therapy. J Allergy Clin Immunol 1983; 72:34-9.

153. Szefler SJ, Brenner M, Jusko WJ, Spector SL, Flesher KA, Ellis EF. Dose- and time-related effect of troleandomycin on methylprednisolone elimination. Clin Pharmacol Ther 1982; 32:166-71.

154. Szefler SJ, Ellis EF, Brenner M, Rose JQ, Spector SL, Yurchak AM, et al. Steroid-specific and anticonvulsant interaction aspects of troleandomycin-steroid therapy. J Allergy Clin Immunol 1982; 69:455-60.

155. Yamashita SK, Ludwig EA, Middleton E Jr, Jusko WJ. Lack of pharmacokinetic and pharmacodynamic interactions between ketoconazole and prednisolone. Clin Pharmacol Ther 1991; 49:558-70.

156. Zurcher RM, Frey BM, Frey FJ. Impact of ketoconazole on the metabolism of prednisolone. Clin Pharmacol Ther 1989; 45:366-72.

157. Rae SA, Williams IA, English J, Baylis EM. Alteration of plasma prednisolone levels by indomethacin and naproxen. Br J Clin Pharmacol 1982; 14:459-61.

158. Kaufman M. Treatment of multiple sclerosis with high-dose corticosteroids may prolong the prothrombin time to dangerous levels in patients taking warfarin. Mult Scler 1997; 3:248-9.

159. Klinenberg JR, Miller F. Effect of corticosteroids on blood salicylate concentration. JAMA 1965; 194:601-4.

160. Wolfe F, Hawley DJ. The comparative risk and predictors of adverse gastrointestinal events in rheumatoid arthritis and osteoarthritis: a prospective 13 year study of 2131 patients. J Rheumatol 2000; 27:1668-73.

161. Buttgereit F, Da Silva JA, Boers M, Burmester GR, Cutolo M, Jacobs J, et al. Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. Ann Rheum Dis 2002; 61:718-22.

162. Jacobs JW, Bijlsma JW. Interpretation of trial methodology not always easy: comment on the editorial by Landewé. Arthritis Rheum 2003; 48:2693-4.

163. Huizenga NA, Koper JW, De Lange P, Pols HA, Stolk RP, Burger H, et al. A polymorphism in the glucocorticoid receptor gene may be associated with and increased sensitivity to glucocorticoids in vivo. J Clin Endocrinol Metab 1998; 83:144-51.

164. Lin CW, Nakane M, Stashko M, Falls D, Kuk J, Miller L, et al. Trans-activation and repression properties of the novel nonsteroid glucocorticoid receptor ligand 2,5-dihydro-9-hydroxy-10-methoxy-2,2,4-trimethyl-5-(1-methylcyclohexen-3-y 1)-1H-[1]benzopyrano[3,4-f]quinoline (A276575) and its four stereoisomers. Mol Pharmacol 2002; 62:297-303.

HYPERLINK 1 to the paper:
Low-dose glucocorticoid therapy in R.A. A review on safety: published evidence and prospective trial data.

Toxicity data from four prospective trials of low-dose glucocorticoid therapy in R.A.

Box 1. Description of Trials

The ARC Low Dose Glucocorticoid Study (ARC)[1;2].

A double blind, randomised controlled trial over 2 years followed by 1 year double blind follow-up in 128 patients with rheumatoid arthritis diagnosed for less than 2 years. Patients had active disease and were allocated equally to prednisolone 7.5mg daily (in specially prepared tablets) or placebo. All other treatments except oral glucocorticoids were permitted and in practice most patients were treated with non-steroidal anti-inflammatory agents and second line anti-rheumatoid treatment.

The "Low-Dose Prednisolone Therapy"Study (LDPT)[3].

In this double blind study 192 patients with active rheumatoid arthritis of duration less than 2 years who had not been treated before with intramuscular gold or methotrexate were equally and randomly allocated to one of two treatment strategies for two years: 1) 5 mg prednisone once daily in the morning and either intramuscular gold (50 mg gold sodium thiomalate/week up to a total dose of 1000 mg, thereafter 50 mg every 2 weeks) or methotrexate (7.5 mg weekly for the first 3 weeks, thereafter 10-15 mg weekly; no folate supplementation) 2) placebo and intramuscular gold or methotrexate as above. Therapy with bisphosphonates, calcitonin, estrogens and fluorides was not allowed.

The Utrecht Prednisolone Trial[4].

In this double blind study 81 patients with rheumatoid arthritis of duration less than 1 year were equally and randomly allocated to one of two groups of treatment for two years: 1) 10 mg prednisone once daily at breakfast, 2) placebo in the same way. NSAIDs and analgesics were permitted and all patients received 500 mg elementary calcium in the evening. After 6 months sulfasalazine rescue medication was permitted.

The West of Scotland Early Rheumatoid Arthritis Trial (WOSERACT)[5].

In this double blind study 167 patients with rheumatoid arthritis of median disease duration 12 months (range 2-84 months) were equally and randomly allocated to one of two groups of treatment for two years: 1) 7 mg prednisolone once daily plus sulphasalazine (dose target 40mg/kg in both arms. Medians

achieved (and range): 2.5g (1-4g) in both arms) 2) placebo prednisolone and sulphasalazine. At 2 years, in the prednisolone group 61 patients were still on prednisolone and 59 patients still on sulphasalazine. In the placebo group at 2 years 65 patients were still on placebo prednisolone and 53 still on sulphasalazine. The use of drugs for prevention of osteoporosis was left to the discretion of the rheumatologist: it was greater in the active group, although physicians were blind to treatment.

Musculoskeletal adverse effects

Osteoporosis

Box 2. Osteoporosis data from trials: Bone loss and fractures

ARC Results[1;2].

Results are available for 21 patients (Prednisolone=11, Placebo=10) who had bone mineral density (BMD) measurement because they were attending study centres where measurement facilities were readily available at the time of the study. Mean (SD) percentage reductions in BMD in the spine of the prednisolone group were 1.61 (4.98) and 2.96 (5.59) after 1 and 2 years respectively while in the placebo group the percentage reductions were 2.27 (5.54) and 1.29 (4.64) (not significantly different). In the hip the prednisolone group percentage reductions were 2.16 (7.07) and 1.19 (3.16) after 1 and 2 years respectively while in the placebo group the percentage reductions were 0.56 (5.62) and 4.02 (2.45) (P=0.04 at 2 years).

LDPT Results[3].

X-rays of the lumbar spine among patients in prednisolone group (n=59) revealed two fractures at baseline, and one additional fracture at 24 months (n=46). Among patients (n=64) in the placebo-group, there were at baseline two fractures, and at 24 months (n=53) two additional fractures. The fractures were located at L1 (n=2), L2 (n=3) and L3 (n=2).

Utrecht Results[4].

In the two years, T-scores mean (se) of the lumbar spine in the prednisone group changed from -0.8(0.3) to -1.1(0.3) and in the placebo group from -0.7(0.3) to -0.6(0.3). For the femoral neck T-scores changed from-1.8(0.2) to -1.9(0.2) and from -1.9(0.2) to -1.9(0.2), respectively. This were all non significant intra and between group differences. So, for the lumbar spine at 2 years, the difference between the T scores

of the two groups was 0,5 in favor of the placebo group; this was unchanged at follow-up at 3 years. At 3 years, the cumulative number of fractures in the spine in the prednisone group was twice that of the placebo-group (10 versus 5). Doubling of the fracture rate has been described for changes in the T score of 1; this suggests that the double fracture rate in the prednisone group was also partly due to structural changes of bone in the prednisone group.

WOSERACT Results[5].

In the 2 years, median lumbar bone density in the prednisolone group changed from 1.079 at baseline to 1.073 g/cm^2; in the placebo group bone densities were 1.157 and 1.280 g/cm^2, respectively. For the femoral neck, bone density in the 2 years changed from 0.900 to 0.881 g/cm^2 in the prednisolone group and from 0.927 to 0.911 in the placebo group. There were no statistically significant differences between the two groups at both points in time, nor statistically significant changes within groups.

Endocrine and metabolic adverse effects

Glucose intolerance and diabetes

Box 3. Hyperglycaemia data from the trials: blood and urine glucose levels

ARC Results[1;2].

No patient in the prednisolone group (n=61) developed diabetes mellitus, but one patient in the placebo group (n=67) did so.

LDPT Results[3].

In the prednisolone group serum glucose levels of 34 patients (per protocol population) were measured 2 hours after the last meal; at baseline and at 2 years, means (se) were the same: 5.6 (0.2) mmol/l. In the placebo group, mean (se) serum glucose levels of 42 patients (per protocol population) were 5.3 (0.2) at baseline and 5.1 (0.2) mmol/l at 2 years. In addition, the values for the so-called intention-to-treat population are given: prednisolone group (n=74): baseline value 5.7 (0.1) and after 24 months 5.6 (0.3) mmol/l, placebo-group (n=81): at baseline 5.9 (0.2) and at 24 months 5.5 (0.3) mmol/l.

Utrecht Results[4].

In contrast to the placebo group, the mean (SD) serum glucose level increased significantly in the prednisone group, from 5.1 (0.6) at baseline to 5.9 (1.9) mmol/l at 2 years, p= 0.01. Hyperglycemia, as

defined by the World Health Organization, developed in 2 patients in the prednisone group (n=40) and 1 in the placebo group (n=41).

WOSERACT Results[5].

One patient in the placebo arm was on treatment for diabetes mellitus at the outset and 2 years. No patient required introduction of this therapy at 2 years (neither in the placebo nor active treatment group).

Endocrine and metabolic adverse effects

Fat redistribution, body weight and growth

Box 4. Weight gain trial data

ARC Results[1;2].

Both groups increased in weight, but there was no statistically significant mean increase in body weight in either group. One patient in the study had relevant weight gain; this patient had been allocated to prednisolone.

LDPT Results[3].

Weight gain was assessed for the intention-to-treat population: 80 patients in the prednisolone group and 85 patients in the placebo group. Body weight in the prednisolone group increased from a mean (se) of 71.7 (1.4) kg at baseline to 76.7 (2.0) kg at 2 years, $p<0.05$; in the placebo group the numbers were 73.1 (1.7) kg at baseline and 73.4 (2.3) kg at 2 years. The difference at two years between the two groups was statistically significant.

Utrecht Results[4].

In the 10 mg prednisone group (trial methodology: see above) body weight increased significantly from baseline: the mean (sd) rose from 77 (19) to 80 (20) kg at 2 years, $p=0.001$; in the placebo group there was no statistically significant difference in time.

WOSERACT Results[5].

In the 7 mg prednisolone group (trial methodology: see above), body weight increased from 68kg at year 0 to 71kg at year 1 and 72kg at year 2 (Wilcoxon 0-1 year and 0-2 year $p<0.001$). In the placebo group weight increased from a median of 69kg at time 0 to 70kg at year 1 and 72kg at year 2 (Wilcoxon 0-1 year

p=0.162, 0-2 year p<0.05). There were no statistically significant differences between the two groups at any point in time.

Cardiovascular adverse effects

Hypertension

Box 5. Hypertension data from Trials

ARC Results[1;2].

On the group level: there were no significant increases in blood pressure in either group. On the patients' level: two patients in the prednisolone group (n=61) developed hypertension versus one patient in the placebo group (n67).

LDPT Results[3].

At the start of the study, mean (se) blood pressure values (systolic/diastolic) were 128(2) / 79(2) mm Hg in the prednisone group (n=34) and 130(3) / 80(2) in the placebo group (n=42). At two years, these numbers were 141(4) / 85(2) and 140(4) / 86(2), respectively: no statistically significant differences between the two groups at both points in time, nor statistically significant changes within the groups. For the intention-to-treat population (prednisolone group n = 80 and placebo group n = 85) the data were as follows. Prednisolone group baseline values:128(2) / 78(1); at 24 months 141(3) / 84(2). Placebo-group baseline values 128(2) / 79(1); at 24 months 140(4) / 85(2). In the prednisolone group 6 patients (6%) developed hypertension (as stated by the physician) compared to 2 patients (2%) in the placebo group.

Utrecht Results[4].

Patients with severe hypertension were excluded from this study. At the start of the study 11 patients in the placebo group and 5 in the prednisone group were normotensive under medication for their essential hypertension and they remained stable during the study. The numbers of patients with newly developed hypertension during the study were about equal: 7 in the prednisone group and 6 in the placebo group.

WOSERACT Results[5].

At the start of the study, median blood pressure values (systolic/diastolic) were 140/80 mm Hg in the prednisone group and 135/80 in the placebo group. At two years, these numbers were 140/80 and 130/80, respectively: no statistically significant differences between the two groups at both points in time,

nor statistically significant changes within the groups. However, the participating rheumatologists were proactive in initiating antihypertensives as required and more patients were on antihypertensives in both the placebo and active groups than at the outset of the study (placebo 12 time 0, 16 at 2 years; active 10 time 0, 13 at 2 years).

Ophthalmological adverse effects

Box 6. Ophthalmological data from Trials

LDPT Results[3].

In the prednisolone group, 3 patients got glaucoma versus no patient in the placebo group; in the prednisolone group, 5 patient acquired cataract versus 6 patients in the placebo group; in both groups, less than 50% of patients was screened for ophthalmologic adverse effects, however.

Utrecht Results[4].

In the prednisone group, 1 patient got glaucoma versus no patient in the placebo group; in both groups, 1 patient acquired cataract.

Gastrointestinal adverse effects

Box 7. Gastrointestinal data from Trials

ARC Results[1;2].

No patient with relevant peptic ulcer disease was reported.

LDPT Results[3].

In this study, patients with recent gastric and intestinal ulcers were excluded. Gastric distress was seen in the prednisolone group (n=93) in 9 patients (10%), versus in 4 patients (4%) in the placebo group. A gastric ulcer was detected in 3 patients in the prednisolone group (3%), but in none of the patients in the placebo group.

So, a higher rate of peptic ulceration and their complications due to low to medium dose glucocorticoids is not supported by these data.

Utrecht Results[4].

In the prednisone group, peptic symptoms leading to gastroscopy occurred in 7 patients versus 3 in the placebo group, but ulcer with bleeding at gastroscopy was found in 1 patient in the prednisone group versus 2 in the placebo group.

WOSERACT Result[5].

One GI bleed occurred in the active steroid group, none in the placebo group. No other patient had relevant peptic ulcer disease.

Infectious adverse effects

Box 8. Infection trial data

Utrecht Results[4].

Seventeen infections, treated with antibiotics occurred in 14 patients in the prednisone group (n=40) over the 2 years versus 22 infections treated with antibiotics in 15 patients in the placebo group (n=41).

WOSERACT Results[5].

No excess of infections was documented in the prednisolone group compared to the placebo group.

References

1. Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. N Engl J Med 1995; 333:142-6.

2. Hickling P, Jacoby RK, Kirwan JR. Joint destruction after glucocorticoids are withdrawn in early rheumatoid arthritis. Arthritis and Rheumatism Council Low Dose Glucocorticoid Study Group. Br J Rheumatol 1998; 37:930-6.

3. Rau R, Wassenberg S, Zeidler H. Low dose prednisolone therapy (LDPT) retards radiographically detectable destruction in early rheumatoid arthritis--preliminary results of a multicenter, randomized, parallel, double blind study. Z Rheumatol 2000; 59 (Suppl 2):II/90-II/96.

4. van Everdingen AA, Jacobs JW, Siewertsz van Reesema DR, Bijlsma JW. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial. Ann Intern Med 2002; 136:1-12.

5. Capell HA, Madhok R, Hunter JA, Porter D, Morrison E, Larkin J et al. Lack of radiological and clinical benefit over two years of low dose prednisolone for rheumatoid arthritis: results of a randomised controlled trial. Ann Rheum Dis 2004; 63:797-803.

HYPERLINK 2 to the paper:
Low-dose glucocorticoid therapy in R.A. A review on safety: published evidence and prospective trial data.

Toxicity of Step-Down Glucocorticoid Therapy in the COBRA Trial

(Authors of this section: Maarten Boers, Arco C. Verhoeven)

Introduction

The spectrum of toxicity of chronic glucocorticoid therapy is exhaustively reviewed in this article. However, less is known about the acute changes in routine monitoring parameters in patients with rheumatoid arthritis (RA). We reanalyzed the monitoring data of the COBRA trial that compared the combination of step-down prednisolone, low –dose methotrexate (MTX), and sulfasalazine (SSZ) to SSZ alone in early RA. This analysis demonstrates the highly consistent changes induced in many of these parameters, but also a relatively low yield in terms of findings requiring changes in therapy.

Methods

The COBRA ("COmbinatietherapie Bij Reumatoide Artritis") trial was a multicenter randomized double-blind controlled trial of 56 weeks duration in patients with early active RA[1]. Application of the exclusion criteria resulted in a fairly healthy group (apart from the RA): we excluded patients aged below 18 or over 70, those with serious comorbidity or recent (3 months or less prior to inclusion) major surgery, with active infectious disease, with a history of tuberculosis, recurrent infections, recent (< 3 months) gastritis or gastrointestinal ulceration, any history of gastrointestinal bleeding or neoplasia. We also excluded patients with diabetes mellitus, hypertension treated with more than one antihypertensive drug, significant cardiovascular disease, liver disease, cataract, glaucoma, hematologic disorders, partial or total colectomy, reduced renal function (creatinine clearance < 50 ml/h), proteinuria (> 0.5 g/day), hypoalbuminemia and chronic dermatitis. Finally, we excluded patients on treatment with phenytoin, phenylbutazone, salicylates, barbiturates, cholestyramine, probenecid, oral anticoagulants (dicumarol derivatives), and patients with a history of alcohol or substance abuse[1].

COBRA treatment comprised a starting dose of prednisolone of 60 mg/day, rapidly tapered to 7.5 mg/day within a time period of 6 weeks, continued unchanged for 20 weeks, and then withdrawn completely after 26 weeks; 2) a low dose of MTX (7.5mg/week in one gift) for 40 weeks, and then withdrawn in 4 weeks; and 3) a maintenance dose of SSZ 2000 mg/day. All patients received folic acid supplements (1mg/day), and calcium supplements (500 mg daily); and/or vitamin-D supplements (25-(OH)-vitamin-D) (400 IE daily) were prescribed if necessary. Patients randomized to the SSZ monotherapy group received a maintenance dose SSZ (2000 mg/day) as well as the supplements mentioned above.

Monitoring schedule. Patients were seen weekly in the first four weeks; then at weeks 6, 9, and 12; and every 4 weeks thereafter. At every visit patients were questioned for adverse events; body weight and blood pressure were recorded. Blood and urine samples were examined: more than 20 tests in total at 19 time points, i.e. almost 400 tests per patient in the 56 weeks of the trial (see results). Bone mass was measured every half year.

Analysis. Results of monitoring per treatment group are presented as mean (95% confidence interval) in line graphs over time. The initial period is magnified to better depict the changes. To correct for baseline differences, body weight is expressed as change. In each graph, the "Null

Zone" indicates the area in which group means should fall if there is no significant difference at the 5% level (two-sided p value >0,05).[2] In other words, observed means falling outside this zone differ significantly from each other. As these analyses are exploratory no correction for multiple testing was applied.

Results

Clinical results. The main findings of the COBRA trial have been published previously[1]. Briefly, COBRA treatment (76 patients) caused almost immediate and strong improvement in disease activity, resulting in similarly strong and significant functional improvement assessed at week 16. Single treatment with sulfasalazine (79 patients) caused lesser but also significant improvement at week 16. Both treatment groups improved further up to week 28. Most of the clinical difference between the groups disappeared when prednisolone was subsequently withdrawn, with no further change after withdrawal of methotrexate. At week 28, the combination therapy group had significantly less progression of radiographic joint damage compared to the sulfasalazine group. Recently we have shown that progression remains slower in the COBRA group up to 4.5 years, i.e. 3.5 years after withdrawal of prednisolone.[3]

Toxicity. Significantly less patients stopped COBRA than sulphasalazine: 6 (8%) versus 23 (29%) (p=0.0008), and COBRA patients dropped out later (Figure 1). Differences were apparent for both toxicity and lack of efficacy. For instance all 4 efficacy dropouts in the COBRA group occurred after week 28, when prednisolone and methotrexate were stopped; in contrast, most of the 19 dropouts in which loss of efficacy played a role in the sulphasalazine group occurred before week 28 (Figure 1). The adverse reactions that led to withdrawal of 2 patients in the COBRA group were: gastrointestinal tract complaints and dyspnea (final diagnosis exacerbation of chronic bronchitis). Adverse reactions that led to withdrawal of 8 patients in the sulphasalazine group were skin rashes in 4 patients, gastrointestinal tract complaints in 2 (one with concurrent proteinuria), granulopenia with concurrent increase in aminotransferases in one patient, and thrombopenia (diagnosis preleukemic disease) in the remaining patient.

The study medication was discontinued and restarted at an adjusted dose according to protocol in 5 patients. Three of these 5 patients (1 from the COBRA group) had low granulocyte counts, the other 2 patients (in the COBRA group) had elevated aminotransferases and gastrointestinal complaints, respectively. The remaining adverse events were not followed by withdrawal of study medication. These included 18 cases (12 COBRA) of infection, treated on an outpatient basis, 17 cases (9 COBRA) of gastrointestinal complaints (no ulcer or bleeding); 10 cases (6 COBRA) of cardiovascular disease; including 1 myocardial infarction; and 11 cases (5 COBRA) of skin disorders. Various other symptoms, signs and transient laboratory abnormalities were reported in 37 cases (20 COBRA).(1) Thus, a total of about 62000 tests (400*155) not including confirmatory procedures were performed to detect relevant toxicity in a total of 7 patients.

Bone mass. In the first 28 weeks, mean (95% c.i.) lumbar bone density change in the COBRA group (n=64) was –1.2% (-2.0,-0.3) versus 0% (-0.9, 0.9) in the sulphasalazine group (n=62) (p=0.06). In 56 weeks, changes were –1.3% (-2.3,-0.4) and –0.3% (-1.4, 0.8) respectively, p=0.15. In the femoral neck corresponding bone density changes over 28 weeks were –0.6 (-2.1, 0.9) versus –0.7 (-2.1, 0.7); over 56 weeks –1.9 (-3.1,-0.7) versus –1,3 (-2.5,-0.1; both: p>0.2. Eight versus 6 patients lost more than 5% (mean 8%) of spinal bone; 14 versus 9 lost more than 5% (mean 8%) of femoral neck bone. These losses typically occurred in the first half year, with stabilisation or improvement thereafter.(1)

Diabetes. For this study, patients with concomitant diabetes mellitus were excluded. In all patients, regularly urinanalysis for glucose was performed; positive glucose reactions were extremely rare.

Weight. Only during the first half year of therapy, the COBRA treatment group in which high to intermediate doses of glucocorticoids were used gained statistically more weight than the sulphasalazine alone group. After about one year (56 weeks), the weight gain from baseline was 1.7 kg in the combined treatment group (in which prednisone had been stopped) and 1.2 kg in the sulphasalazine alone group, a non-statistically significant difference.

Upper GI. In the COBRA trial, patients with a history of gastrointestinal bleeding or recent (<3 months) gastritis or gastrointestinal ulceration were excluded. In the COBRA strategy group and sulfasalazine alone group, gastrointestinal complaints occurred, probably at least due to sulfasalazine and/or methotrexate, but no ulcer or bleeding took place. A relevant finding from the economic study that ran alongside the trial: cost savings occurred because many patients in the COBRA group stopped taking NSAIDs and gastroprotection.

The results of routine monitoring are shown in Figure 2 (blood pressure, weight gain, and selected blood chemistry) and Figure 3 (hematology). In Figure 2 ESR is shown as reference outcome measure for disease activity, and in both the prednisolone dosing schedule is shown at bottom. Apparent from almost all graphs is an almost immediate change in the COBRA group, followed by a slower change in the SSZ group. Within the groups the changes in many measures were highly consistent, resulting in strongly significant differences between the groups. These differences became less and mostly disappeared after the prednisolone was stopped, similar to the main outcome measures. Especially notable are the rapid (but limited) weight gain, the biphasic pattern in the platelet count, the rapid increase in hemoglobin and the increases in serum creatinine in both groups. More in line with expectation is the leukocytosis, granulocytosis, lympho– and eosinopenia. The changes in alkaline phosphatase are mainly attributed to changes in bone turnover, as there were no relevant changes in the liver function tests (gammaglutaryltransferase [GGT] stable; aspartate– and alanine aminotrasferase [ASAT and ALAT] decreased resp. increased slightly in the COBRA group in the first 6 weeks; data not shown).

Discussion

The results of the intensive monitoring schedule in the COBRA trial first of all confirm that RA causes profound disturbances in many physiologic parameters. The documented changes in the trial are the sum of (rapid or slow) improvement in disease activity with reversal of the abnormalities and specific effects of the drugs employed. In the first 4-8 weeks most changes are highly likely caused by the prednisolone dosing scheme. The biphasic platelet response in the COBRA group suggest an acute effect of platelet mobilization caused by prednisolone, followed by the antirheumatic effect which reverses thrombocytosis due to RA. It is less likely that an antirheumatic effect is the cause of the initial rapid increase in hemoglobin: reversal of anemia takes longer. Combined with the increases in creatinine it might be that RA itself causes changes in the distribution of intravascular fluid (i.e. hemodilution) which is reversed by therapy.

The second observation is that in this relatively healthy population the monitoring schedule is fairly inefficient in detecting clinically relevant abnormalities. This is of course a well-known problem in the monitoring of antirheumatic therapy, and one that cannot be solved by observations from randomized trials. Both the selection of the patients and the relative rarity of severe adverse events make it difficult to extrapolate toxicity findings from trials to general practice. Nevertheless, most events that are amenable to detection by lab monitoring occurred in the initial phases of treatment. On the basis of the COBRA experience, we would now suggest a check of body weight, blood pressure and lab (hematology, creatinine, liver function tests; urine for glucose and protein, preferably 2 hours after a meal) at 1 and 3 weeks after the start of therapy. If these tests are normal, there is no necessity for further monitoring other than that

advised for single DMARD therapy. It should be noted that recommendations for such monitoring is mostly based on expert opinion rather than evidence.

In conclusion, early aggressive therapy of RA with step-down glucocorticoids according to the COBRA schedule causes rapid and highly consistent changes in blood pressure, body weight and lab parameters, contrasting with slower changes in patients treated with SSZ monotherapy. These changes are most likely the result of reversal of RA effects combined with intrinsic effects of the drugs in the combination, especially glucocorticoids.

Legends

Figure 1. Patients remaining in trial and reasons for dropout, per treatment arm. COBRA treatment protocol is shown at the bottom of the graph. AE, adverse event; LoE, loss of efficacy; viol, protocol violation.

Figure 2. Line graphs of group means over time: ESR, mean blood pressure, weight gain and selected chemistry tests. The gray area is the "Null Zone", the area where the group means reside when there is no significant difference at the two-sided p of 0.05. The initial period is magnified to better depict the rapid changes in the first weeks. Each vertical grid line equals a 4-week period. The thick grid lines show important changes in treatment schedule: end of step-down prednisolone, start of tapering low dose prednisolone, start of methotrexate tapering.

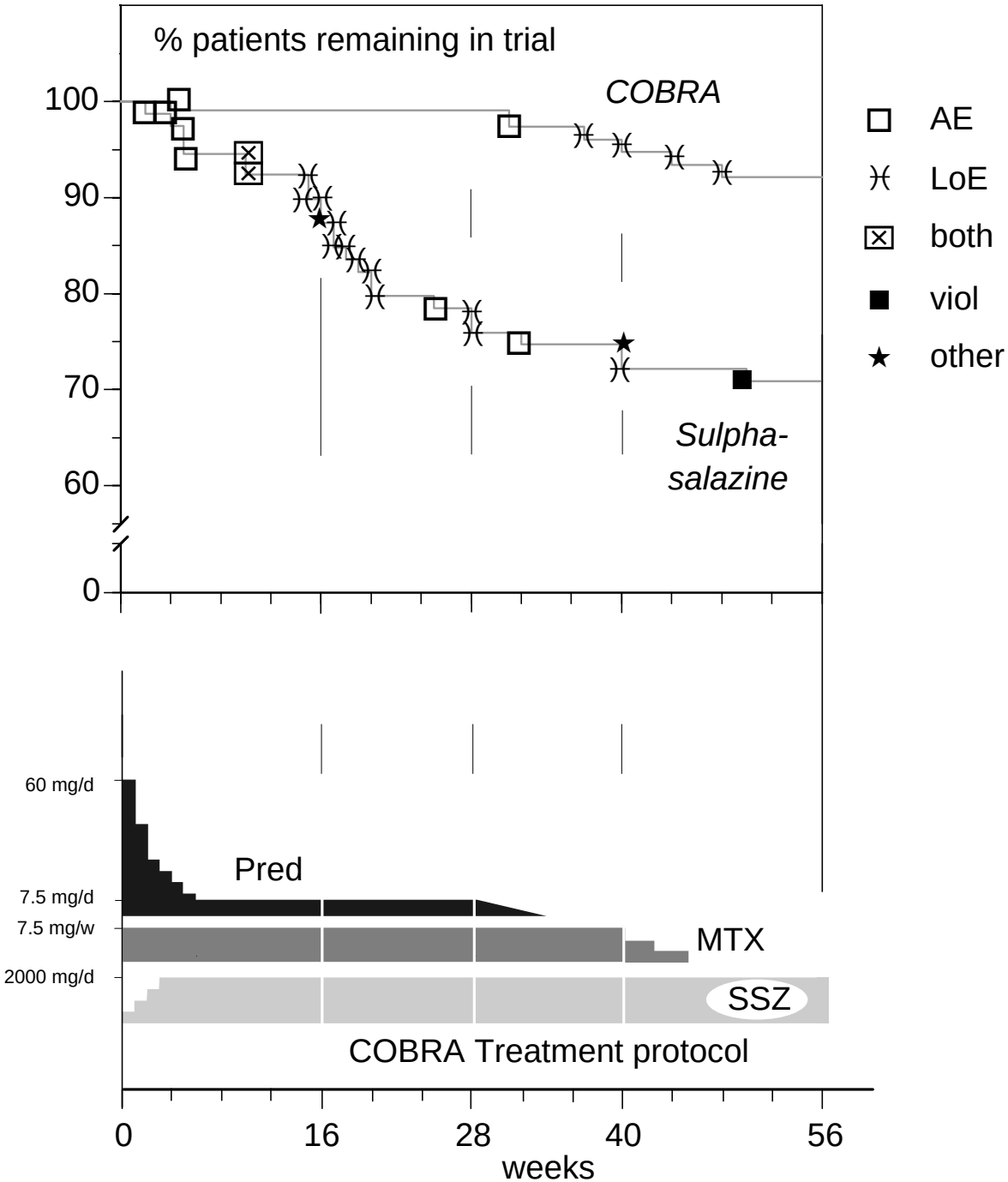
Figure 3. Line graphs of group means over time: hematology tests. Explanations, see Figure 2.

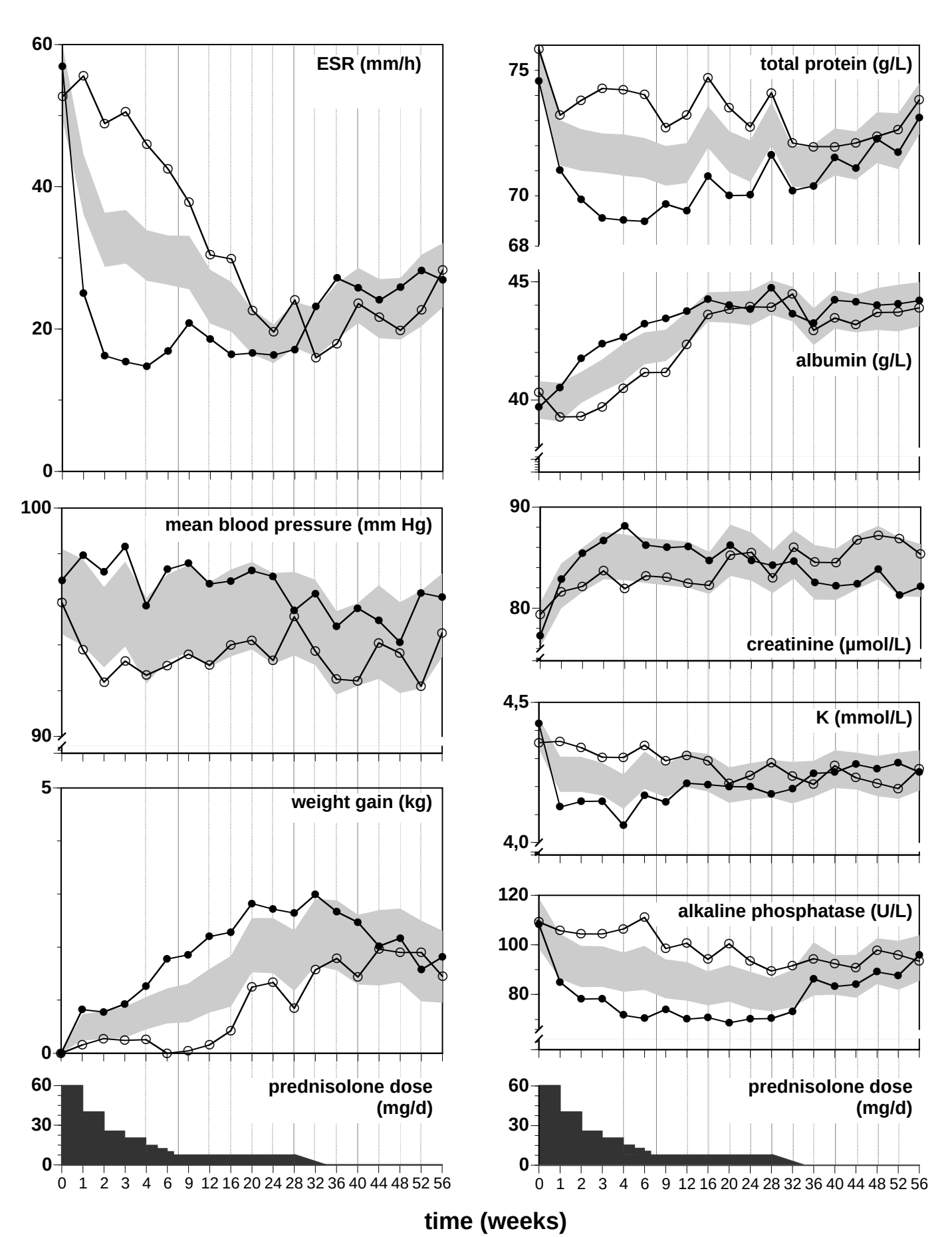
References

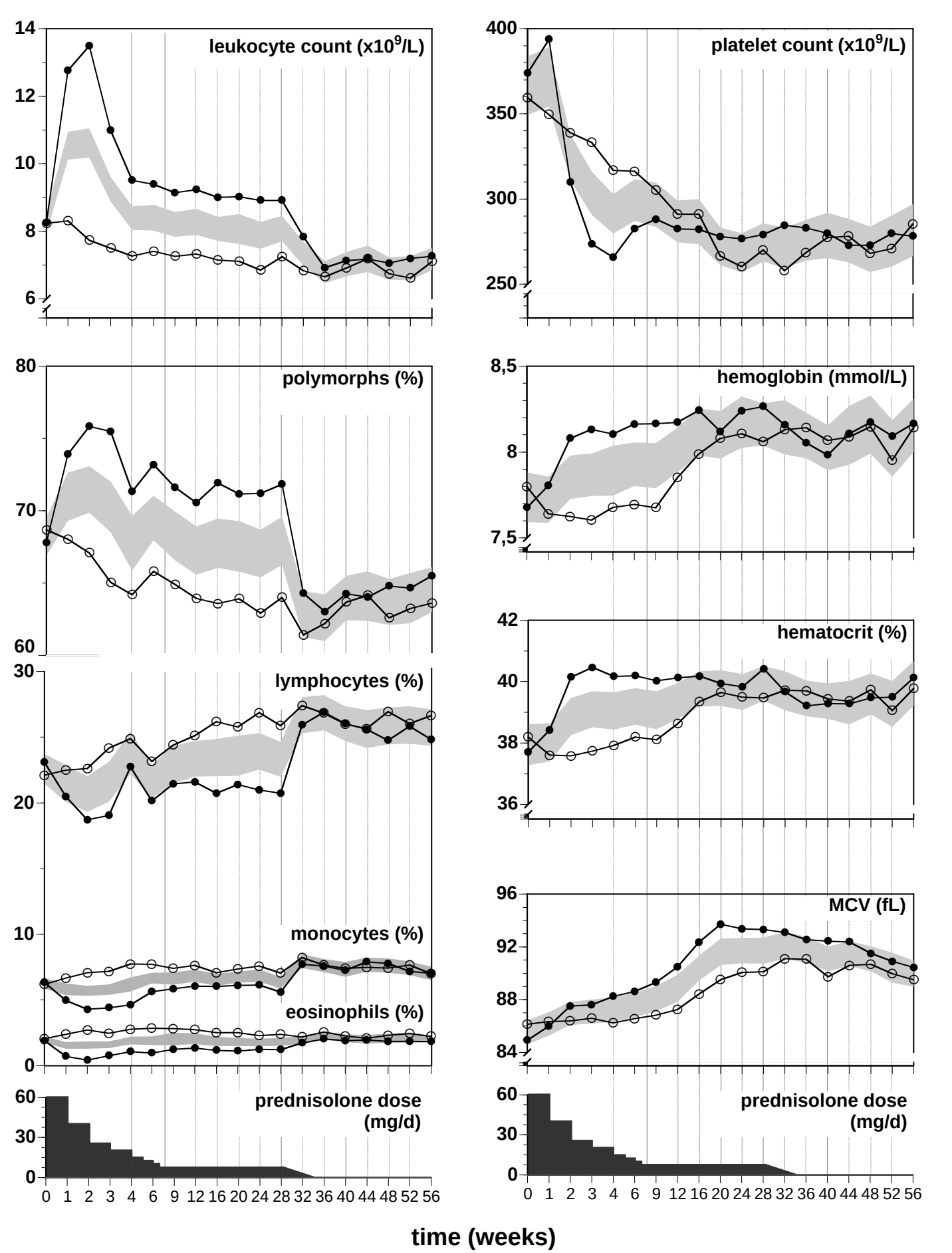
1. Boers M, Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van Denderen JC et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997; 350:309-18.

2. Boers M. Null bar and null zone are better than the error bar to compare group means in graphs. J Clin Epidemiol 2004;57:712-5.

3. Landewe RB, Boers M, Verhoeven AC, Westhovens R, van de Laar MA, Markusse HM, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum 2002; 46:347-56.


% patients remaining in trial
COBRA
Sulpha-
salazine
100
90
80
70
60
0
AE
LoE
both
viol
other
60 mg/d
Pred
7.5 mg/d
7.5 mg/w
MTX
2000 mg/d
SSZ
COBRA Treatment protocol
0
16
28
40
56
weeks


ESR (mm/h)
60
40
20
0
total protein (g/L)
75
70
68
albumin (g/L)
45
40
mean blood pressure (mm Hg)
100
90
creatinine (µmol/L)
90
80
weight gain (kg)
5
0
K (mmol/L)
4,5
4,0
alkaline phosphatase (U/L)
120
100
80
prednisolone dose (mg/d)
60
30
0
prednisolone dose (mg/d)
60
30
0
0 1 2 3 4 6 9 12 16 20 24 28 32 36 40 44 48 52 56
0 1 2 3 4 6 9 12 16 20 24 28 32 36 40 44 48 52 56
time (weeks)


leukocyte count (x10^9/L)
platelet count (x10^9/L)
polymorphs (%)
hemoglobin (mmol/L)
lymphocytes (%)
hematocrit (%)
monocytes (%)
eosinophils (%)
MCV (fL)
prednisolone dose (mg/d)
prednisolone dose (mg/d)
time (weeks)