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REVIEW

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Adverse effects of glucocorticoids have been abundantly reported. Published reports on low dose glucocorticoid treatment show that few of the commonly held beliefs about their incidence, prevalence, and impact are supported by clear scientific evidence. Safety data from recent randomised controlled clinical trials of low dose glucocorticoid treatment in RA suggest that adverse effects associated with this drug are modest, and often not statistically different from those of placebo.

Supplementary information is available at http://www.annrheumdis.com/supplemental

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The introduction of glucocorticoids (GC) in the 1950s was 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 disclosed a spectrum of toxicity that shook the foundations of this treatment. Despite this, GC still have a pivotal role in the management of diverse rheumatic conditions. The proportion of patients treated with GC by practising physicians every day 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 the risk/benefit ratios of this treatment. Arguments against GC use are dominated by fear of a toxicity 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 this fear is justified for lower dose treatment, specifically for patients with RA, has not been completely answered.

To examine this problem, a working party was organised, comprising experts with a special interest in this area, including rheumatologists and one endocrinologist from Europe and America, 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 and the results of these are presented in this paper:

- *A literature review of the adverse effects of long term low dose GC, especially in rheumatic diseases.* The group compiled an extensive and comprehensive list of all putative adverse effects attributed to GC by a primary search of textbooks and review papers. This list was split into categories similar to those in this text. As a first step, for each category a thorough search was performed, using the adverse effects as keywords and the reference lists of the original papers. This literature was reviewed and described; the texts produced were 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 and refers to diverse diseases, doses, and regimens, appreciation of the level of evidence was frequently difficult and subjective. This was resolved by reviewing the underlying data and discussion, until consensus was achieved.
- *An analysis of toxicity data from the randomised controlled trials of GC in RA.* As the working party comprised of representatives of all groups who had conducted 2 year trials on the use of GC in RA, very detailed information on adverse effects from these trials was available for discussion. Differences in methodology precluded a systemic meta-analysis of the adverse effects observed. Here, results from each trial, where available, are summed. The data incorporated in this review come from the following trials: the Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study, here further designated as the ACR study,[1 2] the German study, here further designated as the LDPT (low dose prednisolone therapy) study,[3] the Utrecht study,[4] and WOSERACT[5] (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 described as "the four extensively reviewed trials on low dose GC in RA". More details on these trials are available through hyperlinks to the electronic version of this article on the website of the *Annals* (hyperlink 1, http://www.annrheumdis.com/supplemental). Previously unpublished detailed monitoring results from the "combination treatment in early rheumatoid arthritis" (COBRA) trial are included in the web version of this paper (hyperlink 2, http://www.annrheumdis.com/supplemental).

Abbreviations: BMD, bone mineral density; COBRA, combination treatment in early rheumatoid arthritis (trial); GC, glucocorticoid(s); GI, gastrointestinal; NSAIDs, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus

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 first publication	1995	2000	2002	2004
Reference	1, 2	3	4	5
RA duration at entry (years)	<2	<2	<1	Median 1
Number of patients, prednisolone group	61	34	40	84
Prednisolone dose/day (mg)	7.5	5	10	7
Duration of trial (years)	2	2	2	2
Associated DMARDs	Various	IM gold or MTX	Sulfasalazine rescue	Sulfasalazine

DMARDs, disease modifying antirheumatic drugs; IM, intramuscular; MTX, methotrexate.

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 treatment in lower dosages (⩽10 mg/day prednisolone equivalent) in RA in daily clinical practice.

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 about a ''safe'' dose. Although some studies suggest that doses of 7.5 mg of prednisone a 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 a day.[6–8] Studies focusing on low dose treatment are relatively scarce, however. Further, it is important to recognise 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 regimens have not been shown to reduce bone loss.[9 10]

In 1997, an exhaustive literature search for all prospective studies found only 18 studies and 329 patients in whom bone mass was studied prospectively while receiving 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 a day, the best estimate of bone loss overall in spine and hip (without bisphosphonate treatment) is 1.5% a year. Important positive predictive factors include starting dose and chronic usage; and in the spine, dose and lack of vitamin D supplementation.

> ''Chronic use of glucocorticoids doubles the already increased risk of osteoporosis in RA''

The consequences of this bone mass loss upon fracture rate proved to be quite significant. Although 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 of 2.[13 14] In a recent multicentre cross sectional study, 205 patients with RA who were receiving daily GC orally were compared with 205 matched patients who did not receive GC. Vertebral deformities were found in 25% of patients receiving GC compared with 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 2.5 mg/day 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 increased levels of inflammatory cytokines, such as tumour necrosis factor α, which stimulate differentiation of osteoclasts both directly and indirectly via RANK ligand (osteoclast differentiation factor) and thus lead to bone loss. Possibly, therefore, GC in RA, leading to decreased disease activity, may cause less bone loss than they would have in the absence of inflammatory disease. Studies disagree as to whether a cumulative dose is,[8 16] or is not[15 17] associated with a degree of bone loss. A recent study showed that the greatest increase in the risk of vertebral fractures induced by GC was seen in older postmenopausal women, age being a risk factor independent of bone mineral density (BMD).[18] On the other hand, it is quite likely that, as some studies suggested, fractures occur at higher BMD levels in patients treated with GC than in patients not treated with GC.[19]

Data from the four extensively reviewed trials on low dose GC in RA showed that BMD loss over 2 years of low dose prednisone is not significantly different from that with placebo (hyperlink 1, http://www.annrheumdis.com/supplemental). The higher doses of prednisone used in the COBRA study were associated with a higher BMD loss,[20] but this difference did not reach statistical significance either (hyperlink 2, http://www.annrheumdis.com/supplemental). Fracture incidences were similar in both groups in the LTDP study.[3] However, the Utrecht group found twice the 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 the 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 know whether the treatment or the underlying disease is the cause, because some conditions, such as systemic lupus erythematosus (SLE), are associated with an increased risk of osteonecrosis,[27] especially in young patients with several organs affected. 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 doses are related to more severe underlying disease and increased risk of osteonecrosis. One study reported osteonecrosis in 2.4% of patients receiving GC replacement treatment,[29] but data on low dose GC treatment are scarce and mostly anecdotal. At least in SLE, a higher average dose may be a more important predictor of avascular necrosis of bone than the cumulative dose.[30] No case of avascular necrosis was seen either in the four extensively reviewed trials on low dose GC in RA or in the COBRA trial (hyperlinks 1 and 2, http://www.annrheumdis.com/supplemental).

Many crucial questions in this area remain unanswered—namely, questions about 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 doses of GC, osteonecrosis is uncommon. Primary prevention is not really possible; awareness should be increased.[31]

Myopathy

Remarkably, a search of the literature showed an absence of data on, and proper studies of, myopathy. 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 GC doses of <7.5 mg prednisolone equivalent daily. Chronic steroid myopathy is quite often suspected, but not often found or documented. The clinical picture can be difficult to distinguish from the effects of the underlying disease, especially in the case of musculoskeletal conditions, such as myositis or inflammatory arthritis.[33] On electromyographic examination no spontaneous electrical activity is found; the serum aldolase and creatine kinase 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 preventative or individual risk factors to be evaluated; awareness will facilitate early recognition of this problem. No cases of myopathy were seen in the four extensively reviewed trials on low dose GC in RA (hyperlink 1, http://www.annrheumdis.com/supplemental).

ENDOCRINE AND METABOLIC ADVERSE EFFECTS

Glucose intolerance and diabetes

GC increase serum glucose levels through 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 cause 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 longstanding diabetes.[41 42]

GC related hyperglycaemia is dose dependent. However, low dose GC also have this effect. One case-control study suggested an increased risk (odds ratio = 1.8) for initiation of anti-hyperglycaemic drugs during GC treatment using 0.25–2.5 prednisone equivalent a 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 of developing new onset hyperglycaemia during GC treatment.[41] This is usually rapidly reversed when GC are stopped, 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 four 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 based on the probably inadequate correction for glucocorticoid potency.[47]

Data from the four extensively reviewed trials on low dose GC in RA are quite reassuring in this respect: no cases of new onset diabetes were seen in either of the studies. The Utrecht trial found the least favourable results[4]: a significant increase in mean (SD) 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, hyperglycaemia, as defined by the World Health Organisation, developed in only two patients in the prednisone group (n = 40) and one in the placebo group (n = 41) (hyperlink 1, http://www.annrheumdis.com/supplemental).

There are no preventive measures apart from the use of lower doses of GC. Alternate day treatment 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 dose GC. It is seen even with low dose GC. Potential mechanisms include hyperinsulinaemia, changes in expression and activity of adipocyte derived hormones and cytokines, such as leptin and tumour necrosis factor 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 2 years, in the range of 4–8%. 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, patients in the control groups also gained weight (hyperlinks 1 and 2, http://www.annrheumdis.com/supplemental).

Suppression of sex hormone secretion

GC in high doses decrease gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus, decrease basal and GnRH-stimulated luteinising hormone secretion from the pituitary, and decrease the responsiveness of gonadal cells to luteinising hormone, leading to lower levels of oestrogens[56] and testosterone.[57 58] This latter effect predominates in men.[59] These suppressing effects can contribute to steroid-induced osteoporosis. Despite these observations, it has been suggested that glucocorticoid treatment 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

Dyslipidaemia, atherosclerosis, and cardiovascular disease

GC treatment is considered to be a risk factor for dyslipidaemia and atherosclerosis.[61–64] Several studies in patients with SLE suggest that GC treatment is dose dependently associated with hypercholesterolaemia: significant changes were seen only at prednisone doses higher than 10 mg/day.[65–67] Beyond induction of dyslipidaemia, the role of GC in atherosclerosis is controversial. Longer steroid use is significantly associated with coronary artery disease in patients with SLE.[68–70] Also a study in patients with RA suggested that

GC treatment early in the disease course increased the risk of coronary artery disease.[71] On the other hand, in a study using an animal model of atherosclerosis,[72] although administration of dexamethasone induced hyperlipidaemia, 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 raised C reactive protein and accelerated coronary artery disease offers a theoretical basis for GC benefit on atherosclerotic disease in inflammatory diseases.[73] Furthermore, recent data from cohorts show that RA disease activity unfavourably alters the blood lipid profile, and that 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.

> ''Evidence is lacking to show that low dose GC, unlike high dose GC, significantly increase the incidence of cardiovascular disease in RA''

Recently, a record linkage database study on 68 781 GC users (of whom 1115 patients had RA) and 82 202 non-users 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/day prednisolone long term. However, it was increased in patients using doses ⩾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, the evidence does not support a significant role for low dose GC treatment on the development of cardiovascular disease in RA, in contrast with higher doses. In patients with RA receiving low dose GC, the disease itself seems to be a greater risk factor.

Water and electrolyte balance, oedema, renal and heart function

Hypernatraemia, hypokalaemia, and sodium and water retention are mineralocorticoid effects, produced by endogenous GC at supraphysiological 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 the 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, seen 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 GC treatment with <20 mg/day 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 are very reassuring about the effect on blood pressure: prednisone had no significant effects on blood pressure in any of the trials. During the first phase of the COBRA trial, the mean blood pressure was at some time points higher in the prednisone than in the placebo group, but high to medium doses of GC were used. Note that patients with severe hypertension were excluded from most of these trials (hyperlinks 1 and 2, http://www.annrheumdis.com/supplemental).

These results suggest that glucocorticoid-induced hypertension is dose related and is less likely with medium or low dose treatment. Individual variation in susceptibility and other factors, such as the basal level of blood pressure, diet salt, functional renal mass, associated diseases, and drug treatment, may have 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 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 seen in over 5% of the patients exposed to ⩾5 mg prednisone equivalent for ⩾1 year.[97–99] The incidence of iatrogenic Cushing's syndrome is dose dependent and, in general, becomes evident after at least 1 month of GC treatment.[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 treatment. Cutaneous atrophy mainly results 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 ⩾5 mg prednisone equivalent a day for ⩾1 year.[97 102 103] Wound healing impairment seems uncommon at low dose, but there are no exact data on prevalence. There are no data on the incidence of steroid acne and hair effects like hirsutism and hair loss, but they are more common with long term treatment with medium to high doses of GC, such as those used after organ transplantation.[96] These effects of GC may sometimes be difficult to separate from those of the disease itself (for example, hair loss in SLE) and other medications.

Most of the cutaneous adverse effects of GC are not considered serious by the doctor, but they may represent a considerable cosmetic problem for the patient. Available data suggest that these effects are relatively uncommon and of minor clinical concern with low dose GC treatment, although data on incidence are scarce. There is no strong evidence to support the claim that use of the lowest possible dose and alternate day treatment may fully prevent these adverse effects. 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 the trial duration was relatively short for development of these complications.

OPHTHALMOLOGICAL ADVERSE EFFECTS

Cataract

Long term use of systemic GC may induce formation of posterior subcapsular cataract, characterised 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 incidence of cataract with long term low dose systemic GC treatment are scarce. In a group of patients with RA treated with 5–15 mg/day prednisone (mean (SD) 6 (3) mg/day) for a mean (SD) of 6 (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 treatment reduces the risk.[105] Cataract formation is considered to be irreversible. We could find no evidence of the possibility of halting progression by reducing the dose or interrupting treatment. More careful prospective assessment of cataract formation among GC users is needed to answer this question definitively. In the four extensively reviewed trials on low dose GC treatment in RA and in the COBRA study, excess cataracts were not reported, but the 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 ophthalmological 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, 18–36% of those exposed to GC had an increase in intraocular pressure.[106] Open angle glaucoma was found in 6/32 (19%) rheumatic patients exposed to ⩾7.5 mg/day prednisone equivalent for more than 1 year and in 1/38 (3%) patients treated with <7.5 mg/day prednisone equivalent (Tryc A, Bartholome B, Buttgereit F, *et al*, unpublished data).

However, the occurrence and magnitude of the increase in intraocular pressure with GC administration are highly variable between patients.[107] A high incidence of this adverse effect with GC use 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] A rise in intraocular pressure with exogenous GC is generally reversible when treatment is stopped, 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 are recommended for patients receiving high dose long term systemic GC treatment, especially for those with associated risk factors for glaucoma. For patients receiving low dose GC treatment and who have 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 ophthalmological check in a significant number of patients. However, these checks suggest an increased risk of glaucoma with prednisone (hyperlink 1, http://www.annrheumdis.com/supplemental).

GASTROINTESTINAL ADVERSE EFFECTS

Peptic ulcer disease

The association between GC use and the risk of peptic ulcer disease has been the 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 among current GC users was 2.0 (95% CI 1.3 to 3.0). However, this increased risk was almost completely due to co-treatment with non-steroidal anti-inflammatory drugs (NSAIDs): the relative risk for patients co-medicated with NSAIDs was 4.4 (95% CI 2.0 to 9.7), but for those receiving only GC there was no significant increase in risk: 1.1 (95% CI 0.5 to 2.1). In large scale studies based on the UK General Practice Research Database,[115] the relative risk of upper gastrointestinal (GI) complications was 1.8 (95% CI 1.3 to 2.4) for users of GC compared with 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 than for non-users of either drug. Data from the four RA prospective trials and the COBRA study show 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, http://www.annrheumdis.com/supplemental). 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 postmortem studies suggest that GC use is associated with an increased incidence of pancreatitis. In one postmortem study, acute pancreatitis or fat necrosis was seen in 29% of those treated with adrenocorticotropic hormone or GC compared with 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 patients with SLE.[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 when treatment is interrupted, an observation that may explain the lower infectious risk with the use of short acting GC and alternate day treatment.[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 an increased risk of opportunistic infections, exacerbated by treatment with GC.[124,125] Of the intensively reviewed four studies of low dose GC treatment in RA, both in the Utrecht and the WOSERACT trials, prednisone up to 10 mg/day was not associated with increased incidence of any kind of infections over the 2 years of the trials.[4,5]

In patients treated with GC, physicians should anticipate the risk of infections with both usual and unusual organisms, realising that GC may blunt the classic clinical features and delay the diagnosis. Under special clinical circumstances and in severely immunocompromised 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/day prednisone for 8 weeks have been associated with increased risk in one series.[126]

PSYCHOLOGICAL AND BEHAVIOURAL DISTURBANCES

Steroid psychosis

Psychosis is characterised by hallucinations, delusions, or both. Reported estimates of the incidence of steroid psychosis vary greatly (0–60%), owing to differences in study groups and methodology of assessing this adverse event. Following an authoritative review, the estimate of incidence of 5–6% 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 often 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 41–80 mg/day, and >18% with higher doses. Several studies examining doses of ⩽20 mg did not find cases of psychosis.[129] This adverse event was not reported either in the four extensively reviewed trials on low dose GC treatment in RA, or in the COBRA study.

> ''Psychosis induced by glucocorticoids is rare with low dose regimens''

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 regimens 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 80–160 mg of prednisone equivalent a day, far exceeding common long term regimens in rheumatology.[132] Evidence for minor effects is scarce, but doses of <20–25 mg prednisone equivalent a day are associated with few or no significant disturbances.[133 134] However, individual susceptibility is highly variable and in a few published cases a relationship between low dose GC and even topical steroids and psychotic episodes seems hard to doubt. These adverse events were not reported or systematically assessed in the four extensively reviewed trials on low dose GC treatment in RA, or in the COBRA study.

DRUG INTERACTIONS

Significant interactions between GC and other prescription treatments have been well documented. Drugs that *reduce* the systemic GC concentration may diminish clinical efficacy. They include large doses of aluminium/magnesium hydroxide, which decrease prednisone bioavailability by 30–40%,[135 136] and most anticonvulsant drugs (for example, phenobarbital, phenytoin), which enhance the metabolism of GC.[137–142] Rifampicin accelerates the metabolism of synthetic GC, as may St John's wort.[143] Non-responsiveness of inflammatory diseases to prednisone, induced by rifampicin, has been described and rifampicin-induced adrenal crisis in patients receiving GC replacement treatment 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 suggest that several NSAIDs, including indometacin and naproxen, increase GC concentrations.[157] Conversely, 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 GI adverse events, particularly in patients with RA (see above).[115 160]

Neither the four extensively reviewed trials on low dose GC treatment in RA, nor 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, an extensive review of the adverse effects of four trials on low dose GC treatment in RA and the COBRA study, and extensive group discussions, our 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 treatment. The balance of risks and benefits of low dose treatment clearly differs from that of medium and high dose treatment, for 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. The evidence on which to support clear recommendations about toxicity of low dose GC is surprisingly weak. The literature and the recent trial results suggest that routine toxicity monitoring for patients receiving low dose GC is not currently justifiable or cost effective based on existing evidence. However, patients with additional risk factors (for example, osteoporosis, obesity, hypertension, a family history of diabetes or glaucoma) merit more careful observation (table 2).

GC will probably be used with enormous therapeutic value in the treatment of a large variety of rheumatic conditions for many years to come, especially because 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 the 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 using state of the art end points. 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 undertaken, and physicians might wish to consider these issues in clinical practice when prescribing GC treatment.

Table 2 Glucocorticoid related adverse effects other than osteoporosis that may justify regular checks

- 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 glycaemia control in patients with diabetes mellitus
- Cataracts and glaucoma
- Peptic ulcer (in combination with NSAIDs)
- Hypertension

Furthermore, subjects participating in randomised clinical trials may not have the same disease characteristics or comorbidities as patients treated in the community, thereby limiting the generalisability of findings of this kind of trial.[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 GI 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 to hope that an even better safety/efficacy ratio can be achieved in the future.[164]

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