The safety of low-dose glucocorticoids in rheumatic diseases

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ABSTRACT

Glucocorticoids (GC) remain the most commonly used agents for managing inflammatory rheumatic diseases. The adverse effects (AE) associated with high-dose GCs are well established, but there is a widespread misconception that AEs of high-dose GC therapy (>30mg prednisone or equivalent daily) are similar in low-dose therapy (≤ 7.5mg prednisone equivalent a day). Although high-quality evidence on AEs of low-dose GC therapy is still lacking, risks and safety of low-dose GC therapy in rheumatic diseases are reviewed based on current evidence by category, including musculoskeletal, cardiovascular, infectious, gastrointestinal, neuropsychiatric, endocrine and metabolic, dermatologic, and ophthalmologic AEs. Recommendations concerning monitoring AEs with low-dose GC therapy are provided for each category of AEs on the basis of our literature review and clinical experience. There is emerging evidence that low-dose GCs are associated with a much lower level of AEs, which would allow their use over long periods in patients with rheumatic disease who gain clinical effectiveness and well-being from their use. Nonetheless, knowledge and understanding of AEs from low-dose GCs is vital to maximise benefits and minimise risks to patients.

Introduction

Since the introduction of glucocorticoids (GC) in the 1950s, they have been widely used in a large variety of inflammatory diseases. Adverse effects of high-dose GC are well-established and have limited their use, but these adverse effects are much less common with low-dose GC. In this review, we will focus on low-dose use of GC treatment, defined as a treatment with ≤7.5mg prednisone equivalent a day, but will also extend our review of the literature of GC dosages in a higher range used in the treatment of rheumatic diseases. Of note, GCs in the low does range occupy less than 50% of the glucocorticoid receptors and are less associated with non-genomic effects (1). In this review, we define medium dose as >7.5 mg to 30 mg/day and high-dose GC therapy as >30 mg prednisone or equivalent daily.

After sixty years of GC use in clinical practice, there is a very well-defined spectrum of adverse effects (AEs) associated with high and medium dose GC therapy. By contrast, low-dose AE associations are much more contentious. Although high-quality evidence on AEs of low-dose GC therapy is often scarce and at times conflicting, we present the risks and safety of low-dose GC therapy in rheumatic diseases based on the best current knowledge available.

Since the vast majority of available data on GC is retrospective, efforts have been made recently to define the adverse effects of chronic GC treatment in lower dosages based on randomised controlled trials (RCTs) and prospective cohort studies (2, 3). Although the EULAR Task Force on GCs formulated recommendations for the monitoring of low-dose GC-related AEs, some AEs, such as psychological or behavioural AEs are difficult to systematically assess and all observational data on this topic has persistent problems with confounding (4). Furthermore, it is often difficult to differentiate AEs of low-dose GC therapy from those occurring from the underlying GC-requiring diseases, or other co-morbidities. Specifically, physicians are more inclined to treat patients with more active and severe diseases with GCs, an example of confounding by indication. RCTs eliminate this source of confounding but bring with them the absence of real-world effectiveness, small sample sizes, limited duration of follow-up and often a lack of systematic evaluation of certain AEs. We review relevant data on the occurrence of AEs associated with low-dose GC exposure from RCTs and

Table I. Selected randomised controlled trials of low-dose glucocorticoids (GC).

Author, year (citation)	Study design	Patients (n.)	GC dose	Duration of Follow-up
Laan, 1993 (15)	Prednisone 10 mg (tapering) *vs.* placebo in RA (concomitant IM gold therapy)	20 *vs.* 20	10 mg/day and tapering between 12 and 20 weeks	44 wks
Kirwan, 1995 (12)	Prednisone 7.5 mg or placebo in RA (concomitant DMARD therapy)	61 *vs.* 67	7.5 mg/day for 2 years	2 years
Boers, 1997 (10)	Sulfasalazine/methotrexate/ prednisone (COBRA therapy) *vs.* sulfasalazine in RA	76 *vs.* 79	Initially 60 mg/day, tapered in 6 weekly steps to 7.5 mg/day, stopped at 28 weeks	80 weeks
Hansen, 1999 (11)	DMARD treatment with or without prednisolone (mean daily dose 6 mg) in RA	51 *vs.* 51	Mean 6 mg/day, mean cumulative dose 2160 mg	1 year
van Everdingen, 2002 (9)	Prednisone 10 mg *vs.* placebo in RA	41 *vs.* 40	10 mg/day	2 years
Sheldon, 2003 (16)	Budesonide 9 mg *vs.* placebo in RA (concomitant DMARD therapy)	14 *vs.* 12	7.5 mg/day	4 weeks
Capell, 2004 (7)	Prednisone 7 mg *vs.* placebo in RA (concomitant sulfasalazine therapy)	84 *vs.* 83	7 mg/day	2 years
Kirwan, 2004 (13)	Budesonide 3 mg *vs.* 9 mg *vs.* prednisolone 7.5 mg *vs.* placebo in RA (concomitant DMARD therapy)	37 *vs.* 36 *vs.* 39 *vs.* 31	2.5 mg/day and 7.5 mg/day	12 weeks
Svensson, 2005 (17)	Prednisone 7.5 mg *vs.* no GCs (concomitant gold or methotrexate therapy; NSAID for all patients)	93 *vs.*.96	7.5 mg/day	2 years
Wassenberg, 2005 (18)	Prednisone 5 mg *vs.* placebo in RA (concomitant gold or methotrexate therapy; NSAID for all patients)	93 *vs.* 96	5 mg/day	2 years

by category of AE (5-16). The RCTs included are detailed in Table I.

General determinants of GC adverse effects

The occurrence of AEs is heavily dependent on the dose and duration of GC therapy. Other factors that may influence both the therapeutic benefit and AEs include the patient's age, timing of doses during the day, individual differences in GC metabolism, and rate of GC clearance. A pharmacokinetic alteration seen in the elderly may contribute to the increased incidence of AE from chronic GC therapy in older adults (17, 18). It is believed that giving GCs as a single dose early in the morning, or in an alternate-day regimen, leads to less Cushing's syndrome or pituitary suppression (19). However, alternate-day therapy is usually unsuccessful in controlling the underlying diseases, such as RA.

A threshold dose or duration has not been well described for most AEs of GCs. There appear to be two distinct dose-related patterns of AEs based on self-reported health problems evaluated in 1066 RA patients by Huscher *et al*. A "linear" increase with increasing dose was found for a Cushingoid phenotype, ecchymosis, leg oedema, mycosis, parchment-like skin, shortness of breath, and sleep disturbance.

A "threshold pattern" describing an elevated frequency of events beyond a certain threshold value was observed at medium to high doses for glaucoma, depression/listlessness and increases in blood pressure. Dosages of 5 mg/day or more were associated with epistaxis and weight gain. A very low-dose GC threshold was seen for cataract (<5 mg/day) (Fig. 1) (20).

The underlying GC-requiring disease and co-morbidities are important factors independently associated with GC AEs. While even low-dose GC therapy likely increases osteoporosis risk, the underlying diseases such as RA or SLE, also increases the risk of osteoporosis. Co-morbidities, such as COPD and diabetes, could increase risk of serious infection and altered glucose metabolism, and could lead to polypharmacy with risk for GC drug interactions. Although significant interactions between GCs and other medications have been well documented, there are no adequate prospective studies of these interactions. Patients and rheumatologists have concordant views of most GC AEs, such as osteoporosis, diabetes and cardiovascular diseases. However, frequent but less serious AEs (*e.g.* skin thinning, Cushingoid appearance) may be of greater concern to patients than to physicians (21).

Musculoskeletal adverse effects
Osteoporosis

GC therapy is the most common cause of secondary osteoporosis. Higher dose and longer duration of GC use have shown strong associations between exposure to glucocorticoids and the risk of fractures (22, 23). However, no consensus exists regarding a safe average or cumulative GC dosage with regard to bone, as wide individual variation is seen. The effects of long-term high-dose GCs on bone mineral density (BMD) are clear, but the effects of lower-dose GCs in patients with rheumatic diseases remain somewhat controversial. In most GC RCTs, participants were permitted calcium, vitamin D or hormone replacement therapy. In 2 RCTs (one with mean GC dose 6mg and the other with mean GC dose 10mg and tapering), lumbar BMD was significantly decreased in GC group. However, other RCTs did not reveal significant decreases in BMD or an increased risk of fracture (5, 7-9, 13, 15, 16, 24). In a meta-analysis in 2008, low-dose GC use resulted in a moderate worsening in lumbar BMD compared with controls, whereas femoral BMD was not significantly decreased. Subgroup analysis of BMD data performed on a change-from-baseline basis showed that GCs had a clear effect on both lumbar and
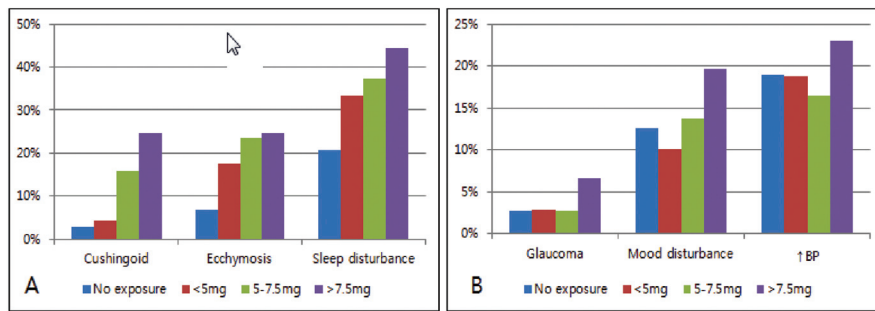
Fig. 1. Two distinct dose-related patterns of adverse events were observed from self-reported health problems relating to dose and duration of glucocorticoid intake in unselected patients with rheumatoid arthritis from routine practice (n=1066). (**A**) Linear pattern, (**B**) Threshold pattern (Adapted from Huscher D *et al.*: Dose-related patterns of glucocorticoid-induced side effects. *Ann Rheum Dis* 2009; 68: 1119-24.)

femoral BMDs (25). However, there are few data on the reversibility of this risk after cessation of GC therapy. In a retrospective cohort study in a general medical practice setting in the United Kingdom (using data from the General Practice Research Database [GPRD]), a dose dependence of fracture risk was observed. With a standardised daily dose of less than 2.5 mg prednisolone hip fracture relative risk was 0.99 (95% confidence interval (CI) [0.82-1.20]) relative to control, rising to 1.77 [1.55–2.02] at daily doses of 2.5–7.5 mg, and 2.27 [1.94-2.66] at doses of 7.5 mg or greater. For vertebral fracture, the relative risks were 1.55 [1.20–2.01], 2.59 [2.16–3.10], and 5.18 [4.25–6.31], respectively. All fracture risks declined toward baseline rapidly after cessation of oral GC treatment (26).

In a recent study of the effect of GC dose on FRAX(R) derived fracture probabilities in a UK setting (using data from GPRD), a new rule was formulated. For very low-dose exposure (<2.5 mg daily of prednisolone or equivalent), the probability of a major fracture decreased by about 20% depending on age, but for doses between 2.5 mg and 7.5mg daily, the unadjusted FRAX value can be used (27). In summary, although osteoporosis may be aggravated by low-dose GC therapy, good quality evidence on this matter is lacking.

Osteonecrosis
Although numerous reports describe osteonecrosis after high-dose GC therapy, it is difficult to determine the relative contributions of the GC treatment and the underlying disease (28). To our knowledge, there is no evidence on the occurrence of osteonecrosis during low-dose GC therapy. In summary, it is generally accepted that in patients treated with low-doses of GC, osteonecrosis is very uncommon.

Myopathy
Comparison of muscle biopsies from 22 RA patients who had been on long-term low-dose GC therapy with 15 patients who never received GCs showed a low proportion of type I fiber, and reduced type I and type II mean fiber areas (29). In a separate study by the same investigative group, compared to patients with RA who had never been treated with GCs, the reduction in knee extensor strength was 37% and 28%, respectively (p<0.001 and p<0.01). The mean walking speed in patients with GC treatment was 0.9 m/s, a 36% reduction compared with patients who had not received GCs (p<0.01) (30).

The clinical picture of GC-associated myopathy can be very difficult to distinguish from the effects of the underlying disease, especially in the case of musculoskeletal conditions. To our knowledge, there are no reports of myopathy in controlled studies with GC therapy less than 10 mg/day prednisone-equivalent, and it is believed that myopathy is exceedingly rare with low-dose of GC therapy (31-35). Although it very rare, GC therapy may trigger attacks of normokalemic or hypokalemic periodic paralysis, indicating that GCs should be administered with caution in patients with periodic paralysis (36).

Cardiovascular adverse effects
Dyslipidemia, atherosclerosis, and ischaemic heart disease
GC treatment, especially high cumulative GC exposure, is regarded as a risk factor for increasing unfavourable lipid profiles and accelerated coronary atherosclerosis (37). In rheumatic diseases, lipid metabolism may be altered by systemic inflammation, environmental lifestyle factors, drug therapy and several genetic factors. Several studies in SLE patients reported an association between treatment with high doses of GCs and development of an atherogenic plasma lipid profile, but these findings may be confounded by indication and the underlying disease (38-40). By contrast, low-dose GC therapy in RA patients generally is associated with an increase in HDL, without increasing LDL or triglyceride – changes which may be favourable (41-43). To date, RCTs have not identified low-dose GC therapy as an additional risk factor for dyslipidemia (5, 6).

In a cross-sectional study of 398 patients with RA (44), metabolic syndrome was present in 40.1% of patients; the prevalence in patients with no GC exposure was 37.9%, *versus* 40.7% with long-term low-dose exposure, *versus* 50% with long-term medium-dose exposure (p=0.241). The odds ratio (OR) for metabolic syndrome comparing medium-dose with low-dose (OR = 1.64; 95% CI 0.92–2.92) (44) was higher though not statistically significant. In a recent systematic literature review (45), low-dose GC in RA patients showed a protective effect on serum lipid profile but no effect on atherosclerosis. Increased CV events are observed in rheumatic patients who were exposed to higher cumulative exposure, higher average daily dosage of GC (46, 47). In the above systemic review of low-dose GC therapy (45), somewhat in contrast with the lipid findings, four out of six studies reviewed found that low-dose GC therapy was associated with major cardiovascular (CV) events, including myocardial infarction [hazard ratio (HR) = 1.7; 95% CI 1.2–2.3], stroke (OR = 4.36; 95% CI 1.60–11.90 for GC between 6 and 10 mg/day), mortality (HR = 2.03; 95% CI 1.25–3.32) and a

composite index of CV events (in the group of rheumatoid factor-positive RA, HR = 2.21; 95% CI 1.22–4.00). However, two studies did not find any significant association between low-dose GC exposure and mortality (OR = 2.25; 95% CI 0.29–102.5) or a composite index of CV events (OR = 1.3; 95% CI 0.8–2.0). Although the literature reviewed did not show statistically significant associations between low-dose GC exposure and CV risk factors, a trend of increasing major CV events was identified (45). Thus, the effects of low-dose GC on atherosclerosis and progression of CV disease remains incompletely characterised.

Water and electrolyte balance, oedema, heart failure, and hypertension
GCs at high doses can cause hypernatremia, hypokalemia, a marked anti-natriuresis and expansion of extracellular fluid and plasma volume. They raise blood pressure in men and animals through mineralocorticoid effects (48). However, synthetic GCs (prednisone, prednisolone, and dexamethasone) have little mineralocorticoid effect and induce kaliuresis and natriuresis without any change in plasma volume (49, 50). Data on the occurrence of oedema during low-dose GC treatment is scarce, although there was a linearly rising frequency of leg oedema with increasing dose in self-reported health problems (no GC in past 12 months, <5mg/day, 5–7.5mg/day,>7.5mg/day 9.5%, 11.6%, 20.2%, 26.2%) (7, 20, 51).
Although most RCTs do not comment on heart failure, low-dose GC treatment in RA was not associated with development of heart failure or death from heart failure in one RCT (n=81, 2 years follow-up) (7, 16). Follow-up of 195 patients undergoing low-dose GC therapy did not show any relationship between change of blood pressure and either dose of corticosteroid or duration of therapy (52). RCTs also did not reveal an increased risk of hypertension in patients treated with low-dose GCs (5, 7, 8, 10, 11, 16). It is important to note that the studies we identified did not document use of special measurements evaluating blood pressure, oedema, or electrolyte disorders with low-dose GC therapy. Thus, there remains uncertainty about the association of low-dose GCs with changes in blood pressure and water balance.

Infectious adverse effects
GC therapy is strongly associated with an increased risk of serious infections in patients with rheumatic diseases, with increased risk associated with increased doses (53). However, disease severity is an important confounding factor for the GC-associated infectious complications observed in clinical practice. In a total of 7971 patients with RA enrolled in the Consortium of Rheumatology Researchers of North America (COR-RONA) registry who were prescribed methotrexate (MTX), TNF antagonists or other disease-modifying anti-rheumatic drugs (DMARDs), low-dose prednisone use overall was not associated with risk of infection (54). However, low-dose prednisone and TNF antagonists (but not MTX) increased the risk of opportunistic infections.
In a meta-analysis of 71 controlled clinical trials involving over 2000 patients randomly allocated to systemic GCs in the setting of different diseases, a relative risk for the overall infectious complications was 1.6 (95% CI 1.3–1.9). The rate was not increased in patients given a daily dose of less than 10 mg or a cumulative dose of less than 700 mg of prednisone (55). By contrast, a recent systematic review identified 15 studies assessing infection risk of low-dose GC therapy in RA patients and did not find consistent associations between infection risk and low-dose GC treatment (56). In a double blind RCT over 12 weeks in 143 patients with active RA comparing budesonide 3 mg daily, budesonide 9 mg daily, prednisolone 7.5 mg daily, and placebo, Kirwan *et al*. reported that respiratory infection and viral infections were more frequently observed in the GC group (respiratory infections in 17/112 in GC group *versus* 1/31 in placebo group; viral infection in 5/112 in GC group *versus* 0/31 in placebo group) (11). However, a RCT of 242 patients with early active RA comparing 7.5 mg/day prednisolone or no prednisolone for two years reported no significant difference in pneumoni-

tis and fever between two groups (15). Most of the RCTs report only serious infections in rheumatic diseases, and the association between GCs and common non-serious infections is not well-studied, especially in the elderly. In a nested case-control analysis based on cohort of 16,207 patients with RA aged over 65 years from administrative data, GC therapy was associated with an adjusted RR of 1.20 (95% CI 1.15–1.25) for non-serious infection. A dose response was seen; the adjusted RR increased from 1.10 (<5 mg/day) to 1.85 for doses greater than 20 mg/day. While the RR is low at 1.20, the absolute risk was high with one additional infection seen for every 13 patients treated with GCs for 1 year (57). In summary, the literature suggests the risk for infections could be increased in low-dose GC users.

Gastrointestinal adverse effects
Peptic ulcer disease
The relationship between non-steroidal anti-inflammatory drugs (NSAIDs) and peptic ulcer disease is well established. However, the literature on GCs is more limited than that on NSAIDs, and the association between GC use and risk of peptic ulcer disease has been controversial (58, 59). In a nested case-control study that included 1415 patients who were admitted for gastric or duodenal ulcer or for upper gastrointestinal haemorrhage of unknown cause, and 7063 control subjects randomly selected from Medicaid, the estimated RR for the development of peptic ulcer disease among current users of oral corticosteroids was 2.0 (95% CI 1.3–3.0). However, persons concurrently receiving GCs and NSAIDs had a risk for peptic ulcer disease that was 15 times greater than that of non-users of either drug [concurrent NSAIDs user estimated RR 4.4 (95% CI 2.0–9.7); NSAID non-users RR 1.1 (95% CI 0.5–2.1] (60).
In a nested case-control analysis using data from GPRD in United Kingdom (61), the overall adjusted OR for upper gastrointestinal complications associated with current use of oral GCs alone was 1.8 (95% CI 1.3–2.4) compared with non-users. Concurrent use of GCs with low-medium and high NSAID

doses, respectively, produced ORs of 4.0 (95% CI 1.3–12.0) and 12.7 (95% CI 6.2–26.1), compared with non-users (61). A more recent case-control study based on the Health Improvement Network UK primary care database showed that, compared with low-dose aspirin monotherapy, the risk of upper GI bleeding was significantly increased when low-dose aspirin was co-administered with high-dose oral GCs (RR 4.43; 95% CI 2.10–9.34); this was not apparent with low-dose oral GCs (RR 1.01; 95% CI 0.58–1.77) (62). To our knowledge, RCTs with low-dose GC therapy did not reveal an increased incidence of upper GI ulcers or bleeding, but not all clinical trials reported on NSAID co-medication (7, 16). In summary, peptic ulcer disease is a rare complication of low-dose GC therapy without concomitant use of NSAIDs, and it should not be considered an absolute contraindication when GC therapy is indicated (63).

Pancreatitis
Although high-dose GC therapy is implicated as one of many potential causes of pancreatitis, evidence for such an association is weak. In a case series of 8 patients over a 10-year period with pancreatitis and SLE, all 8 patients received therapeutic doses of GCs as part of their treatment for SLE and pancreatitis. All patients manifested both clinical and biochemical resolution of their pancreatitis with the administration of GCs (64). No RCTs with low-dose GC therapy identified pancreatitis, but these studies have been relatively small and systematic assessment for occult cases, such as via biochemical abnormalities, was not part of these investigations. In summary, the risk of developing pancreatitis is probably very low and not independently associated with low-dose GC therapy.

Neuropsychiatric adverse effects
High-dose GC therapy has been associated with a variety of neuropsychiatric side effects such as insomnia, depression, hypomania or euphoria, confusion, and memory problems. There is substantial variability in reported incidence of neuropsychiatric AEs largely

because of unpredictable reactions, the wide range of GC doses, diverse patient groups, and differences in methodology of assessing these AEs. In a meta-analysis of 11 uncontrolled studies involving 935 adult patients, severe psychiatric reactions were reported in approximately 5% of steroid-treated patients, and mild to moderate reactions occurred in about 28% (65). The Boston Collaborative Drug Surveillance Program monitored 718 prednisone-treated patients and recorded a 1.3% (6/463) incidence of psychiatric disturbance at 40 mg/day or less, 4.6% at 41–80 mg/day, and 18.4% with more than 80 mg/day (66).
Although disturbances of mood, cognition, sleep, and behaviour as well as frank delirium or even psychosis are possible, the most common adverse effects of short-term GC therapy are euphoria and hypomania. By contrast, long-term therapy tends to be associated with depressive symptoms (67). In a case-control study of 20 patients receiving long-term low-dose GC (prednisone, 7.5mg/day for >6 months) and 14 control subjects, twelve (60%) of 20 GC-treated patients met diagnostic criteria for a lifetime prednisone-induced mood disorder (68). In a self-report of health problems relating to dose and duration of GC intake of 1066 patients with RA, sleep disturbance increased linearly with increasing dose and depression/emotional lability were reported more frequently at dosages greater than 7.5 mg/day (Fig. 1) (20).
In a prospective cohort of 92 patients with SLE, factors predictive of psychosis were low serum levels of albumin, complement, and creatinine; history of anxiety disorders; and a family history of psychiatric illnesses. However, after multivariate adjustment, only hypoalbuminemia remained significant (69).
In a self-reported health problems relating to dose and duration of GC intake of 1066 patients with RA, Huscher *et al*. recently showed that sleep disturbance increases linearly with increasing dose and depression/ emotional lability were reported more frequently at dosages of over 7.5 mg/day (Fig. 1) (20). In a double blind RCT by Kirwan *et al*. as described above, depression and mood swings were more frequently reported

in GC group (depression in 20/112 in the GC group *vs*. 4/31 in placebo group; mood swings in 16/112 in GC group *versus* 6/31 in placebo group) (11). However, the exact incidence of such symptoms in rheumatic patients who received low-dose GC therapy cannot be determined from clinical trials. The literature on the prevention and treatment of potential GC-induced adverse psychiatric effects is poorly developed (70).
In summary, GC-induced psychiatric AEs are unpredictable in individual patients, although dosage appears related to the incidence of adverse effects but not to the timing, severity, or duration of these effects.

Endocrine and metabolic adverse effects
Diabetes and glucose intolerance
Medium- to high-dose GC therapy is well established to cause impaired glucose tolerance and insulin resistance. In a case-control study of 128 SLE patients who were categorised as prednisone non-users (n=41), low-dose (n=71), and medium-dose users (n=16), daily medium-dose GC use but not low-dose use increased insulin levels and insulin resistance (71). In one population-based case control study, the odds ratio for development of hyperglycemia requiring treatment in patients using 0.25–2.5 mg prednisone equivalent a day was 1.77, and the magnitude of risk increased substantially with increasing GC dose (72). In a RCT of 32 healthy men who were allocated to prednisolone 7.5 mg once daily (n=12), prednisolone 30 mg once daily (n=12), or placebo (n=8) for 2 weeks, prednisolone significantly increased fasting plasma glucose levels in a dose-dependent fashion, and was associated with a more pronounced increase of postprandial levels (73).
Outcomes of RCTs with low-dose GC therapy reporting on the development of diabetes and increase of blood glucose levels are conflicting, and most publications have reported only mean glucose levels, limiting insight into clinical relevance (7, 10, 15, 16). Development of new-onset diabetes after starting low-dose GC treatment is rare,

but progression of preceding glucose intolerance to diabetes is more possible (4). To our knowledge, no studies are available on the specific effects of low-dose GC in diabetic patients.

Weight gain and fat redistribution
The incidence of iatrogenic Cushingoid syndrome is dose-dependent and, in general, does not become evident until after at least 1 month of GC therapy (74). The development of Cushingoid features (fat redistribution, buffalo hump, and moon face) and weight gain are particularly displeasing to patients (75). Therapeutic doses of GC induce obesity primarily by increasing energy intake, an effect which may be related to the capacity of GCs to act directly or indirectly on the central regulation of appetite (76). In an observational study by Huscher *et al*. described above, dosage of 5 mg/day or greater was associated with weight gain, and frequency of Cushingoid features was linearly associated with increasing dose (Fig. 1) (20). In a population-based assessment of 2466 long-term GC users, all AEs demonstrated a strong dose-dependent association with cumulative GC use. Among users of low-dose therapy (n=670), increasing duration of use was significantly associated with weight gain (90-day increase in duration of use, OR.1.09, 95% CI 1.01-1.18) (75). In RCTs with low-dose GC, increase in body weight and development of Cushingoid features are described but the data are conflicting (5, 7, 8, 11, 16). Although diminished Cushingoid side effects with alternate-day treatment were observed in liver transplant recipients (77), the only established preventive measures are shorter and lower doses of GC.

Interference with hypothalamic-pituitary-adrenal axis hormone secretion
GCs in high doses suppress the hypothalamic-pituitary-adrenal (HPA) axis, alter hypothalamic gonadotropin-releasing hormone (GnRH) secretion, and decrease basal and GnRH-stimulated luteinizing hormone secretion from the pituitary, leading to decreased oestrogen and testosterone.

It is uncertain whether a patient who has taken less than 10 mg of prednisone or its equivalent per day has HPA axis suppression or not. In a study of double blind RCT by Kirwan *et al*., as described above, low doses of a GC resulted in depression of baseline and ACTH-stimulated cortisol levels after 12 weeks of therapy, although the responsiveness of the HPA axis in individual patients generally remained within the normal range (12). If withdrawal of GCs is indicated, gradual reduction in dose is appropriate for these patients, especially those who have a Cushingoid appearance.
The effect of chronic GC therapy on serum testosterone and oestrogen level predominates in old men and reductions in circulating estradiol concentrations could be implicated in the pathogenesis of GC-induced osteoporosis in men (78, 79). However, data from clinical trials with low-dose GC are scarce, and this question has not been systematically studied.

Dermatologic adverse effects
Most of the cutaneous AEs – including skin atrophy, acne, purpura, easy bruisability, impaired wound healing – are not considered serious by the physician, but they are among the most common AEs reported by the patient (2, 20). Catabolic effects on the skin, including skin atrophy and formation of telangiectasia, mainly result from the effect of GC on keratinocytes and fibroblasts. GC-associated purpura is often observed in the sun exposed areas of the dorsum of the hand and forearm. It is believed that decreased vascular structural integrity is probably a key determinant of purpura and easy bruisability in GC-treated patients (80).
In a self-reported health survey assessing the dose and duration of GC intake of 1066 patients with RA (20), an increased frequency of bruising was reported even in patients taking less than 5 mg/day of GCs over a course of over 6 months (17.4%) compared with the group with no GC exposure in the previous 12 months (6.8%). Bruising was increased with higher dosage (Fig. 1) (20). Delayed wound healing seems uncommon at low-dose, but there are

no strong data on prevalence. RCTs with low-dose GC therapy have not reported on the occurrence of skin atrophy. To our knowledge, there is little or no evidence supporting an increased occurrence of acne, hirsutism, and alopecia during low-dose GC therapy (7, 11, 15, 16). Skin thinning and bruising appear the only common AEs during low-dose GC therapy.

Ophthalmologic adverse effects
Cataract
GC-induced cataracts usually occur in a posterior subcapsular location, often bilaterally. They characteristically involve aberrant migrating lens epithelial cells, and a central posterior location (81). Cataracts often occur after prolonged GC use but disagreement exists concerning effects of total dose, intensity of dose, and duration of administration on cataract formation.
In an observational study of 112 RA patients on low-dose (6.1±3.1 mg/day) long-term (6.2±4.6 years) prednisone, 15% were found to have cataracts, compared with 4.5% of 112 matched RA patients not using prednisone (82). However, an increased risk for cataract was not reported in RCTs with low-dose GC therapy, and most studies are dependent on self-reported data (7, 16). There is no evidence that alternate day treatment reduces the risk and it is believed that cataract formation is irreversible.

Glaucoma and increased intraocular pressure
It is well known that GCs increase the risk of glaucoma by raising the intraocular pressure (IOP) when administered exogenously, and in certain conditions of increased endogenous production (*e.g.* Cushing's syndrome). The incidence of increased IOP with GC tends to increase in persons with preexisting glaucoma, age over 40 years, or certain systemic diseases (*e.g.* diabetes mellitus, high myopia), as well as among relatives of patients with primary open angle glaucoma (POAG) (83). In an observational study of 3792 RA patients enrolled in the German National Database (NDB) (20), glaucoma was found in 3.4% of RA patients who were not exposed to GC in past 12 months

Table II. Glucocorticoid adverse event monitoring recommendations.

Adverse event	Monitoring recommendations
Musculoskeletal	
• Osteoporosis	Follow national guidelines (84) but consider the underlying disease as a key co-factor in osteoporosis development
• Osteonecrosis and myopathy	No specific monitoring recommended
Cardiovascular (CV)	
• Dyslipidemia, atherosclerosis	Standard assessment of CV risk factors required
• Electrolyte disturbances	
• Hypertension	
Infectious	Standard care with heightened vigilance for infectious sequelae and encourage patients to seek prompt medical care for febrile illnesses
Gastrointestinal	
• Peptic ulcer disease	Avoid concomitant use of NSAIDs
• Pancreatitis	No specific monitoring recommended
Neuropsychiatric	No specific monitoring recommended
Endocrine and Metabolic	
• Diabetes and glucose intolerance	No specific monitoring recommended
• Weight gain and fat redistribution	Gradual dose reduction for persons with a Cushingoid appearance
• Interference with hormone secretion	No specific monitoring recommended
Dermatologic	No specific monitoring recommended
Ophthalmologic	
• Cataract	No specific monitoring recommended
• Glaucoma	Indentify other risk factors and educate patients

versus 4.6% of RA patients who were exposed to GC >7.5 mg/day for more than 6 months. In the same database, the frequency of self-reported glaucoma from 1066 RA patients increased only at a dosage greater than 7.5 mg/day (20). Data from clinical trials are conflicting and endpoints are not adequately defined, although ophthalmologic examination in 2 year follow-up showed increased incidence of glaucoma (n=166, 3 in GC group, 0 in placebo group) (7, 16).

Conclusion

Although there is growing evidence from prospective studies and RCTs, the frequency of many adverse events (AEs) associated with low-dose GC use still remains elusive. Overall fear of low-dose GC toxicity is prevalent among physicians, but this may be overestimated based on the existing guidelines and what is currently known. Given the fact that GCs have disease-modifying potential, clear guidelines about toxicity of low-dose GC are required. The EULAR Task Force on GCs formulated recommendations for the monitoring of low-dose GC-related AEs, based on reports of GC-related AEs. However, despite the endemic use of low-dose GC therapy in rheumatic diseases, evidence on the toxicity of low-dose GC is surprisingly weak and data from appropriately designed clinical trials is still lacking for most AE outcomes. From our literature review and clinical experience, Table II provides brief summary of our recommendations on monitoring AEs with low-dose GC therapy. As is true in nearly all areas of medicine, care for persons using GCs in the rheumatic diseases should be patient-centered to maximise benefit and minimise individual risk.

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