Glucocorticoids in systemic lupus erythematosus

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Received and accepted on August 27, 2011.

Clin Exp Rheumatol 2011; 29 (Suppl. 68): S126-S129.

Key words: corticosteroids treatment, systemic lupus erythematosus, pulses, treatment withdrawal, damage

Competing interests: none declared.

ABSTRACT

Glucocorticoids (GCs) remain the cornerstone of the treatment of systemic lupus erythematosus (SLE), despite advances in immunosuppressive drugs, therapeutic protocols and development of new drugs. GCs rapidly control disease activity in mild as well as in severe disease, although these effects might not be maintained over time. The majority of SLE patients have received GC treatment; in some cohorts up to 80% of patients continue this treatment indefinitely as "maintenance" therapy, at low doses of less than 7.5 mg/day. The positive effects of GCs are diminished by adverse effects, particularly at high doses. The cumulative dose of GCs clearly is related to adverse effects. Several unresolved issues in GC treatment of SLE include the optimal doses to be used in induction and maintenance, and in particular how high the dose for how long. It remains unclear whether GCs should be continued indefinitely and, if not, when and how this treatment should be discontinued. Both clinical trials and observational data will help to clarify these issues.

Introduction

The first reports of glucocorticoid (GC) use in the treatment of systemic lupus erythematosus (SLE) date back to the 1950s, shortly after their administration to patients with rheumatoid arthritis (RA) (1, 2). The introduction of these drugs has changed the natural history of SLE, and contributed greatly to the improvement of prognosis observed over the past decades (2).

GC are used in the treatment of acute SLE as well as in the maintenance of remission and are often continued long-term. Zonana-Nacach *et al*. reported in 2000 that, among 539 patients followed at the Hopkins Lupus Cohort, only 11% had never been treated with GCs and 57% of patients with a disease duration >10 years had always received these agents (3). Of 215 SLE patients regularly followed at our Unit in Pisa, only 1 patient has never received GC treatment; 86% of patients have been treated with GCs continuously, with a median maintenance dose of 4 mg/day (methylprednisolone) and mean cumulative dose of 24.7 grams (range 0.5–140 grams) (unpublished data).

Mode of administration and protocols

The most commonly used GCs in the treatment of SLE are prednisone (PDN) and methylprednisolone (MP); other GCs such as triamcinolone and dexamethasone are used less frequently (4).

Although GCs have been administered in divided doses, particularly at medium to high doses, single morning administration appears advisable to minimise both adverse effects and suppression of the pituitary axis (5).

Therapeutic protocols of GCs for SLE range from low (0.1–0.2 mg/kg/day), to medium (0.2–0.5 mg/kg/day), to high doses (0.5–1 gm/kg/day) and intravenous pulses (doses ranging from 250 to 10000 mg/daily for 3 consecutive days) and are used for induction and maintenance of remission (4).

Low-dose GCs (0.1–0.2 mg/kg/day) are generally used as maintenance treatment, often even in the absence of active disease. Low to medium (0.2–0.5 mg/kg/day), doses are also used in the treatment of mild disease activity, particularly cutaneous, muscoloskeletal, haematological and constitutional manifestations.

In patients with mild to moderate SLE flares, two approaches to administration of GCs include: an increase in daily oral dose, followed by rapid tapering; or an intramuscular (i.m.) triamcinolone injection (100 mg). Petri *et al*. reported the effectiveness of i.m. GC to control disease activity, compared with a Medrol dose pack (24 mg tapered of 4 mg each day for a cumulative dose of 84 mg) (6).

Bootsma *et al*. suggested in 1995 that administration of medium doses of GC

might prevent the occurrence of flares in patients whose anti-dsDNA antibody titre was increased (7). More recently, Tseng *et al*. have reported a significant reduction in severe flares among patients treated with moderate dose GCs (30 mg/day for 2 weeks, 20 mg/day for 1 week, 10 mg/day for 1 week) upon presentation with an increase of C3a and anti-dsDNA antibodies (8). Unfortunately, these are the only studies, of which the authors are aware, concerning intervention in patients with clinically inactive but serologically active disease (9).

Pulse GCs have been used since the 1970s to obtain a rapid control of activity in severe disease while minimising toxicity. Intravenous methylprednisolone (MP) appears more immunosuppressive than oral MP, as it has a more prolonged duration of action and induces more profound or sustained changes in neutrophils, lymphocytes, and humoral immunity (10, 11).

Most of the data available concerning pulse GCs in SLE involve treatment of lupus nephritis (LN) (11-18). Early studies suggested that treatment with pulse GCs increased renal survival. Controlled trials from the NIH have reported use of intravenous pulses of 1 gram of MP for three consecutive days in association with cyclophosphamide (CYC), which has become the standard of care for the induction of remission of LN (12-16). Other studies have documented efficacy with lower GC pulses. In the Euro-Lupus Nephritis trial, Caucasian patients with LN were treated with three consecutive pulses of 750 mg each (16). In a study by Moroni *et al*., GC doses were defined on the basis of patients' weight (500 mg each for patients who weighed ≤50 kg; 1000 mg each for patients who weighed >50 kg) (17).

Pulse GCs have been effective in the treatment of non-renal SLE, including haematological, mucocutaneous and articular manifestations (10, 19-21). Macworth-Young *et al*. have added pulse steroids to conventional GC treatment in patients with active disease, and documented more rapid improvement with a relatively safe profile. Although no differences between conventional treatment and pulse GCs were observed after 28 days, nonetheless these data confirm the rapidity of action of pulse GCs, which may be important to prevent long-term damage. Long-term outcomes were not examined, as the study included only 6 months of observation after treatment. Pulse GCs have been effective in the treatment of neuropsychiatric lupus, although combination with CYC was more efficacious than treatment with GCs alone.

Although the dose of 1000 mg daily for three consecutive days is the dose most widely used in clinical practice as well as in clinical trials, it appears possible that lower doses might be as effective (10, 19, 21, 23). In 1987, Edwards *et al*. observed that small doses (100 mg) and high doses (1000 mg) yielded similar efficacy, with lower incidence of adverse effects in patients treated with lower GC doses (19). Bashda *et al*. showed similar efficacy of low (1–1.5 gr) and high (3–5 gr) doses pulse methylprednisolone over three days, but a 3.8-fold higher risk of infectious side effects in patients treated with higher doses. Interestingly, serious infections appeared more common in patients with lower albumin levels. It has been suggested that side effects of GCs may increase with lower albumin levels, and the authors suggested that a reduction of the dose of pulse GCs should be considered in such patients (21). Nonetheless, as low albumin levels also are markers for more severe disease, the increased incidence of side effects could also be related with SLE itself (21).

Tapering schedules for GCs are based primarily on the physician's experience and clinical judgment. In the National Institute of Health (NIH) protocol for the treatment of lupus nephritis (LN), after three pulses of methylprednisolone (MP, 1000 mg/day for three days), patients were given oral prednisone (PDN) 0.5 mg/kg/day for 4 weeks and the dose was then tapered by 5 mg every other day each week to a dose of 0.25 mg/kg every other day, or the minimal dose required to control extra-renal disease (12-15). In the Euro-Lupus Nephritis trial, after three MP pulses of 750 mg/day each, steroids were tapered to PDN 0.5 mg/kg/day or 1 mg/kg/day for 4 weeks and then tapered by 2.5 mg/day every 2 weeks, to reach a maintenance dose of 5–7.5 mg/day (16). At our clinic, after GC pulses patients receive GCs at doses of 0.5 mg/kg/day which are tapered by 8 mg each week to a dose of 16 mg; thereafter, GCs are tapered more slowly, to reach a maintenance dose of 4-8 mg/day in three months.

Topical corticosteroids

Topical GCs are the mainstay of treatment of cutaneous manifestation of lupus erythematosus, although. few controlled studies have been reported. High-potency corticosteroid cream (*e.g*. 0.05%, flucinonide) has been shown to be more effective than low-potency corticosteroid cream (1% hydrocortisone) in the treatment of discoid lupus erythematosus (24). As topical GC treatment may lead to skin atrophy and telangectasia, the treatment should be intermittent and short.

Corticosteroids and SLE pregnancy

PDN and MP are largely metabolised by the placenta, and less than 10% of the maternal dose reaches the foetus. By contrast, fluorinated GCs (betamethasone and dexamethasone) are less metabolised and reach the foetus (25, 26). Therefore, PDN and MP should be used during pregnancy for maternal treatment, while fluorinated GCs should be used to treat foetuses.

Low-dose PDN and MP treatment may be continued safely during pregnancy in patients with SLE. In addition, patients should be advised not to stop GCs treatment without consulting their physician once pregnancy is diagnosed. Flares of disease activity during pregnancy usually are treated with an increase in GC dose to achieve rapid control of disease activity (27).

During pregnancy, GC treatment increases the risk of gestational diabetes and infections, as well as premature rupture of membranes. Therefore, the dose should be maintained as low as possible (as in most clinical situations). In the case of resistant flares, steroid-sparing agents (immunosuppressive drugs, intravenous immunoglobulins) should

be considered (26, 27), though with extreme caution in pregnant patients.
Data have been reported that exposure to GCs at conception may increase the risk of cleft palate; however, it is likely that this risk is minimal (25, 26).
As in the general population, fluorinated GCs are used to treat foetuses when early delivery is threatened to reduce the risk of respiratory distress, cerebral haemorrhage, and death. In addition, in anti-Ro positive patients dexamethasone is used to treat congenital heart block (CHB). Concerns have been raised regarding possible deleterious effects on children's neuropsychological development; a recent study of 11 children with CHB who had been treated with dexamethasone did not show any negative effect (28)
Small amounts of GCs are present in breast milk of lactating women treated with PDN or MP, and consumption by the nursing infant is considered safe.

Side effects and monitoring

Most SLE patients accrue damage related to long-term GC treatment (2, 29-36). Cumulative doses of corticosteroids, irrespective of the route of administration, is predictive of osteoporotic fractures, coronary artery disease, and cataracts. In addition, the risk of avascular necrosis and stroke appears increased in association with high-dose prednisone treatment (2).
The more common side effects of GCs in low (<7.5 mg/day) to moderate doses (7.5-30 mg/day prednisolone equivalent) are osteoporosis, diabetes, cataracts, thinning of the skin, weight gain and fat redistribution. At higher doses, infections, myopathy, psychological disturbances and osteonecrosis are seen (29-31). The effects of GCs on bone mass occur very early after treatment initiation. The risk of osteoporosis and fracture is related with the cumulative dose and he duration of treatment, and therefore in long-term therapy there may be no entirely "safe" dose. Adherence to guidelines on the prevention of glucocorticoid-induced osteoporosis is strongly recommended (9).
Treatment with GCs is associated with an increased risk of infection, again related to dose; this risk appears to be low in patients taking low daily doses. Infections represent a leading cause of death in SLE, and their occurrence has been related both to immunosuppressive treatment and to the disease itself (9). High-dose GC therapy may also increase the risk of cytomegalovirus (CMV) infection. CMV infection may mimic active SLE, and might be frequent with high-dose corticosteroid therapy used to treat active SLE. Therefore, CMV testing (antigenemia) should be considered in selected cases, particularly in patients with active disease undergoing therapy with high-dose GCs (9). Furthermore, assessment for the presence of chronic infections (tuberculosis, hepatitis B and C viruses) should be included in endemic areas (9, 24).
Assessment and correction of comorbidities and/or side-effects – especially diabetes, osteoporosis, peptic ulcer, glaucoma/cataract, peptic ulcer – should be addressed before and during treatment.
Patients receiving chronic therapy who undergo surgery are at risk to develop adrenal insufficiency, and therefore should receive glucocorticoid replacement therapies.

Withdrawal of treatment

SLE patients frequently are maintained on a low dose of GCs (10 mg/day or less of prednisone or equivalent) for years (2). Of 215 SLE patients followed at our Unit, only 30 (14%) had discontinued GC treatment at the last observation. In 2003, Gladman *et al*. suggested that during the first year of disease about 58% of damage could be related to GC use, as compared to about 80% of damage at later stages of disease (32). Although some of the developed damage could indeed be attributed to active disease, nonetheless these data highlight the important impact of GC treatment in damage development.
Therefore, it is important to define not only when and how GCs should be used in SLE treatment but also if, when and how these drugs should be discontinued, after obtaining a stable clinical status of remission.
In a recent survey, Walsh and colleagues showed the presence of extreme variation in practice patterns of GC therapy after induction of remission in patients with diffuse proliferative glomerulonephritis (37), suggesting continued uncertainty on whether long-term treatment is beneficial or not.
Moroni *et al*. reported a retrospective study of 44 patients with diffuse proliferative glomerulonephritis who had been stabilised, in whom treatment was stopped; 12 had flares, but the remaining 32 patients did not show signs of renal or extra-renal activity. The authors concluded that discontinuation of treatment could be appropriate in patients with persistent remission of renal disease, after at least 5 years of treatment. Discontinuation should be very gradual, and monitoring should be very strict (38). No other data on GC withdrawal for non-renal manifestations are available in the literature.

Conclusions

Although many drugs have been introduced in the treatment of SLE, GCs still represent a cornerstone in the treatment of SLE in all its clinical aspects and different levels of severity. In severe disease, pulse GCs appear able to rapidly control disease activity, although their effect is not maintained in the long term and therefore immunosuppressive drugs are required.
However, long-term GC treatment carries a risk of adverse effects, with the development of consistent morbidity. Therefore, GCs may be viewed as a double-edged sword in the treatment of SLE and are one of the first drugs that the treating physician is willing to withdraw in long-term treatment.

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