Rate of Adverse Effects of Medium- to High-Dose Glucocorticoid Therapy in Systemic Lupus Erythematosus: A Systematic Review of Randomized Control Trials

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Rate of adverse events of medium-to high dose glucocorticoid therapy in Systemic Lupus Erythematosus: a systematic review
Abstract

The efficacy of glucocorticoids (GCs) in treating Systemic Lupus Erythematosus (SLE) is beyond doubt. However, GCs-related adverse events (AEs) are multiples and serious. Despite the current available evidences suggesting to reduce daily doses of prednisone <7.5 mg/day, or even to withdraw it, in the real-life practice, it is not uncommon to see patients receiving medium doses (up to 30 mg/day prednisone or equivalent) or high doses (≥30 mg/day). In this systematic review we assessed the rate of AEs related to medium or high dose of GCs in patients with SLE, analysing randomised control trials with at least one of the treatment groups including GCs alone at medium doses or high doses. We found a rate of 9/100 patients/year for hyperglycaemias/diabetes, 25/100 patients/year infections, and 12/100 patients/year for avascular necrosis of the hip. Interestingly, when adjusting for CGs dose and treatment duration, we observed no difference in terms of AEs rate comparing patients receiving medium Vs. high doses. In the era when treat-to-target strategies have been proposed in order to control SLE disease activity, improve health-related quality of life, and reduce morbidity and mortality, using GCs in a more restrictive way should be a goal to prevent major complications in patients with SLE.
INTRODUCTION

Glucocorticoids (GCs) are among the most potent immunosuppressive and anti-inflammatory drugs. Their efficacy in treating Systemic Lupus Erythematosus (SLE) is beyond doubt. However, GC-related side effects are multiples and serious. Indeed, prednisone use has been consistently shown to increase irreversible damage in lupus patients, a major predictor of morbidity and mortality [1]. Despite the current available evidences suggesting to reduce daily doses of prednisone <7.5 mg/day, or even to withdraw it, sometimes physicians might struggle in achieving this goal. Among others, Gladman et al. when reporting on the course of an inception SLE cohort prospectively followed-up of at least 15 years showed that overall 87.7% of patients received GCs, at a mean maximum dose of 37.7 mg/day [2]. Similarly, in the real-life practice, it is not uncommon to see patients receiving medium doses (up to 30 mg/day) or high doses (≥30 mg/day). Adverse effects (AEs) of GC therapy, such as increased risk of infection, avascular osteonecrosis, osteoporosis, myopathy, diabetes mellitus or cushingoid features, as well as skin bruising and cataracts are known and have been well described, especially in studies conducted when GCs were among the few therapeutic tools for SLE management [1]. However, quantifying the risk of AEs related to medium or high dose of GCs is still challenging, especially in an era when patients are rarely receiving GCs alone.

MATERIALS and METHODS

When attempting to assess the rate of AEs related to medium or high dose of GCs in patients with SLE, using a pre-defined protocol, we systematically reviewed the literature selecting studies for evaluation when they met all of the following criteria: (i) Randomized Control Trials (RCTs), (ii) enrolled adult patients with SLE, (iii) at least one of the treatment groups includes corticosteroids alone at medium doses (up to 30 mg/day prednisone or equivalent) or high doses (≥30 mg/day prednisone or equivalent), (iii) reporting rate of GC-related side effects (including hypertension, diabetes, reduction in bone mass index/aseptic osteonecrosis). We searched the MEDLINE, EMBASE and CINAHL databases from their inception (starting in 1950) to December 2016. Medical subject headings (MeSH) terms used in the MEDLINE database search included ‘systemic lupus erythematosus’,
‘corticosteroids’, ‘glucocorticoids’. Index terms were modified appropriately for the other databases. The Cochrane Library (the Cochrane Central Register of Controlled Trials and the Cochrane Database for Systematic Reviews) was also searched. This was supplemented by manually searching bibliographies of these articles and of previously published reviews.

Potential studies identified with the above search strategy were exported to an electronic reference management software program (RefWorks v.2.0). Duplicate studies were identified and removed using the filter functions "exact duplicates" and "close duplicates."

Quality assessments of the suitable RCTs and data extraction from them were done independently by two reviewers (E.M. and S.S.). In case of disagreement, consensus was aimed for and if it was not achieved, a third reviewer (M.J.C.) gave final judgment. It was pre-determined that the corresponding author of an included RCT would only be contacted if any data/information relevant to this meta-analysis was found missing in the published RCT.

We abstracted data for the AEs from every paper and entered them into a Microsoft Excel database. For the 8 retained studies [3–10], the extracted data included study characteristics (setting, duration, design, treatment/intervention, patients characteristic, AES rate and details).

**RESULTS AND DISCUSSION**

Out of one-hundred and two screened studies, a total of 8 RTCs [3–10] met the inclusion criteria, including 182 SLE patients receiving GCs alone at medium doses (up to 30 mg/day prednisone or equivalent) or high doses (≥30 mg/day prednisone or equivalent). Study details, patients characteristics and treatments protocols are shown in Table 1. AEs for each study are described in Table 2. When pooling together the adverse events reported in studies and adjusting for treatment duration, we found a rate of 9/100 patients/year for hyperglycaemias/diabetes, 25/100 patients/year infections, and 12/100 patients/year for avascular necrosis of the hip. Among the studies reporting the type of infection, respiratory tract and herpes zoster infections seemed the most frequently occurred. When adjusting for CGs dose (meant as prednisone equivalent, calculated according to Shimmer et al. [11]) and treatment duration, we observed no difference in terms of AEs rate comparing patients
receiving medium vs. high doses. This observation is in line with the ideas that GCs-related AEs should be considered according to the level of activation of the genomic and non-genomic ways (low doses, up to 7.5 mg/day vs. medium-high doses, equal or higher than 30 mg/day)[12]. This aspect should be kept in mind when a steroid tapering scheme is planned, as it should aim to achieve dose <30 mg/dl to really impact on the rate of GCs-related AEs.

Every effort should be made to avoid GC side effects. It should be remembered that medium to high GCs doses are not the therapy of lupus, but part of the treatment of few severe lupus manifestations. Concomitant use of immunosuppressive agents [13], biological drugs [14,15] and anti-malarials [16] may help keep daily doses of prednisone <7.5 mg/day, or even to withdraw it. In the era when treat-to-target strategies have been proposed in order to control disease activity, improve health-related quality of life, and reduce morbidity and mortality, using GCs in a more restrictive way should be a goal to prevent major complications in patients with SLE.
REFERENCES


<table>
<thead>
<tr>
<th>Study (First Author, Year)</th>
<th>RTC</th>
<th>Country</th>
<th>Inclusion Criteria</th>
<th>Patients</th>
<th>Age mean(range)</th>
<th>Time receiving GCs</th>
<th>Diseases Duration of SLE mean(range)</th>
<th>Steroids (Oral or IV)</th>
<th>GCs Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austin et al. (2009)</td>
<td>Randomized, controlled trial of prednisone, cyclophosphamide, and cyclosporine in lupus membranous nephropathy. USA Membranous LN with ≥ 2 g/d proteinuria</td>
<td>42 (15 in the prednisone group)</td>
<td>40 yrs (13-60)</td>
<td>1 yr</td>
<td>7 months (1 - 120)</td>
<td>oral</td>
<td>High-dosage alternate-day oral prednisone (initiated at 40 mg/m² body surface area [approximately 1 mg/kg body wt] every other day for 8 wk, followed by gradual tapering [5 mg/wk] to 10 mg/m² body surface area every other day for the remainder of the 1-yr protocol treatment period)</td>
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<tr>
<td>Barile-Fabris et al. (2005)</td>
<td>Controlled clinical trial of IV cyclophosphamide versus IV methylprednisolone in severe neurological manifestations in SLE. Mexico NPSLE manifestations*</td>
<td>32 (Cy n=39, MP n=13)</td>
<td>CyC arm: 33 yrs (17–48); MP arm: 26 yrs (19–44)</td>
<td>1 yr</td>
<td>CyC arm 4.2 (0.13–16); MP 2.5 (0–12)</td>
<td>oral and IV</td>
<td>Basal prednisone dose (mg/day) mean (range): AT BASELINE: Cy 45 (15–60); MP 45 (15–60)</td>
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<tr>
<td>Gourley et al. (1996)</td>
<td>Methylprednisolone and cyclophosphamide, alone or in combination, in patients with LN. USA LN</td>
<td>82 (MP arm, n=27; CyC arm, n=27; MP+CyC arm, n=28)</td>
<td>MP arm: 30; CyC arm:30; MP+CyC arm: 31</td>
<td>1 yr</td>
<td>MP arm: 31 ± 8.6 months; CyC arm: 24 ± 6.9 months; MP+CyC arm 39 ± 13.6 months</td>
<td>oral and IV</td>
<td>IV: Bolus therapy with MP (1 g/m² body surface area), given monthly for at 1 year. ORAL: 0.5 mg/kg per day for 4 weeks. The prednisone dose was then tapered by 5 mg every other day each week to the minimal dose of 0.25 mg/kg every other day</td>
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<tr>
<td>Belmont et al. (1995)</td>
<td>Misoprostol and prednisone treatment of LN. USA LN</td>
<td>14</td>
<td>35 ± 2 (range 26-55)</td>
<td>3 months</td>
<td>N/R</td>
<td>oral</td>
<td>Oral prednisone 1 mg/kg/day during 8 weeks. After that, the steroid dose was tapered by 10 mg every 2 weeks for the next 4 weeks</td>
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<tr>
<td>Study</td>
<td>Intervention</td>
<td>Location</td>
<td>Disease</td>
<td>n</td>
<td>Treatment Details</td>
<td>Age of onset (yr)</td>
<td>Outcomes</td>
<td></td>
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<tr>
<td>Barron et al. (1982)</td>
<td>Pulse methylprednisolone therapy in diffuse proliferative lupus nephritis.</td>
<td>USA</td>
<td>LN</td>
<td>N/R</td>
<td>22 (high dose group n=15; pulse group n=7)</td>
<td>11.4 ± 3.6; high dose 11.9 ± 2.9</td>
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<tr>
<td>Boumpas et al. (1992)</td>
<td>Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis</td>
<td>USA</td>
<td>Severe LN</td>
<td>65</td>
<td>N/R 3 months IV of 1.0 g/m2 methylprednisolone over initially in three daily doses, followed by monthly single doses for 6 months</td>
<td></td>
<td>33 months</td>
<td></td>
<td></td>
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<tr>
<td>Edwards et al. (1987)</td>
<td>Double blind controlled trial of methylprednisolone infusions in SLE using individualised outcome assessment</td>
<td>UK</td>
<td>Severe SLE</td>
<td>20</td>
<td>N/R 6 months IV 3 daily infusions of either 100 mg or 1 g of methylprednisolone + a mean of 7mg/day prednisone</td>
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<tr>
<td>Hahn et al. (1975)</td>
<td>Azathioprine plus prednisone compared with prednisone alone in the treatment of SLE. Report of a prospective controlled trial in 24 patients</td>
<td>USA</td>
<td>Severe SLE</td>
<td>13</td>
<td>N/R 3 months Oral Prednisolone 60 mg/day</td>
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</tbody>
</table>

GCs, glucorticoids; LN, lupus nephritis; SLE, Systemic Lupus Erythematosus; NPSLE, Neuropsychiatric Systemic Lupus Erythematosus ; IV, intravenous infusion; CyC, cyclophosphamide; MP, methylprednisolone; N/R, not reported; *peripheral/cranial neuropathy, optic neuritis, transverse myelitis, brainstem disease, refractory seizures or coma
Table 2: Adverse Effects reported in each RTC included in the systematic review

<table>
<thead>
<tr>
<th>Study (First Author, Year)</th>
<th>Patients Receiving GCs alone</th>
<th>Diabetes/Hyperglycaemia</th>
<th>Infections</th>
<th>Avascular necrosis of the hip</th>
<th>Other AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austin et al. (2009)</td>
<td>15</td>
<td>1 Diabetes</td>
<td>1 pneumonia, 3 other infections*</td>
<td>**</td>
<td>N/A</td>
</tr>
<tr>
<td>Barile-Fabris et al. (2005)</td>
<td>13</td>
<td>1 Hyperglycaemia</td>
<td>8 Urinary tract and 4 respiratory infections</td>
<td>N/R</td>
<td>Pancreatidis</td>
</tr>
<tr>
<td>Gourley et al. (1996)</td>
<td>27</td>
<td>N/R</td>
<td>1 herpes zoster, 2 other infections</td>
<td>6 Avascular Necrosis</td>
<td>2 Amenorrhea</td>
</tr>
<tr>
<td>Belmont et al. (1995)</td>
<td>7</td>
<td>N/R</td>
<td>1</td>
<td>N/R</td>
<td>N/A</td>
</tr>
<tr>
<td>Barron et al. (1982)</td>
<td>22</td>
<td>N/R</td>
<td>N/R</td>
<td>3 Aseptic necrosis</td>
<td>N/A</td>
</tr>
<tr>
<td>Boumpas et al. (1992)</td>
<td>65</td>
<td>N/R</td>
<td>3 herpes zoster</td>
<td>3/17 osteonecrosis</td>
<td>6 cataracts</td>
</tr>
<tr>
<td>Edwards et al. (1987)</td>
<td>20</td>
<td>Raised serum glucose levels were transient and not associated with symptoms.</td>
<td>N/R</td>
<td>N/R</td>
<td>Blood pressure rose temporarily in some patients but did not require treatment</td>
</tr>
<tr>
<td>Hahn et al. (1975)</td>
<td>13</td>
<td>7 hyperglycaemia</td>
<td>7</td>
<td>1 Aseptic necrosis</td>
<td>11 Cushingoid habitus; 11 hypertension; 6 hypokalemia</td>
</tr>
</tbody>
</table>

GCs, glucorticoids; N/R, not reported; *other infections included sinusitis, bronchitis, otitis media, dental abscess, upper respiratory tract infection, sty, pelvic inflammatory disease, cholecystitis, and herpes simplex virus skin infection; ** not distinguishing between severe osteoporosis/avascular necrosis of the hip