INPLASY

Efficacy and Safety of Reduced-Dose Glucocorticoids During the Induction Phase of Lupus Nephritis: A Systematic Review of Randomized Controlled Trials

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Fernández Oviedo, G; Nieto Castillo, JP; Forero Ilera, E; Flórez-García, V.

Corresponding author:
Gabriela Fernandez Oviedo

gabrielaf@uninorte.edu.co

Author Affiliation:
Universidad del Norte.

ADMINISTRATIVE INFORMATION

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INTRODUCTION

Review question / Objective In adult patients (>18 years) with Class III, IV, or V lupus nephritis undergoing induction therapy, is the use of reduced-/low-dose oral glucocorticoids (0.5 mg/kg/day) as effective and safe as standard-/high-dose oral glucocorticoids (1 mg/kg/day)?

Rationale Lupus nephritis (LN) is one of the most severe manifestations of systemic lupus erythematosus (SLE), a chronic autoimmune disease characterized by immune dysregulation, autoantibody production, and immune complex deposition in multiple organs. Approximately 40–60% of patients with SLE develop renal involvement during the course of the disease, and LN remains a major cause of morbidity and mortality. Patients with Class III, IV, and V LN are at particularly high risk of progressive kidney damage, with 10–30% developing chronic kidney disease or kidney failure within 10 years, depending on histologic subtype and treatment response. Similar epidemiological trends have been reported in Colombia, where lupus represents an important public health problem and LN is among the leading causes of glomerular disease requiring kidney biopsy.

The treatment of LN consists of two sequential phases: induction and maintenance. The goal of induction therapy is to rapidly suppress renal inflammation, achieve remission, and prevent irreversible renal damage. For decades, high-dose oral glucocorticoids (approximately 1 mg/kg/day), usually combined with intravenous methylprednisolone pulses and immunosuppressive agents such as mycophenolate mofetil or cyclophosphamide, have constituted the standard of care. Although glucocorticoids exert potent anti-inflammatory and immunosuppressive effects that are essential for disease control, their clinical benefits are accompanied by substantial treatment-related toxicity.

Prolonged exposure to high-dose glucocorticoids is associated with numerous adverse effects, including hyperglycemia, glucocorticoid-induced diabetes, hypertension, osteoporosis, fragility fractures, obesity, Cushing syndrome, cataracts, avascular necrosis, and a significantly increased risk of serious and opportunistic infections. Importantly, observational studies have demonstrated that up to half of the irreversible organ damage accumulated in patients with SLE may be attributable to glucocorticoid exposure rather than disease activity itself. Consequently, reducing glucocorticoid-related toxicity has become a major therapeutic objective in the management of SLE and LN.

Over the past decade, advances in immunosuppressive and biologic therapies have encouraged the development of glucocorticoid-sparing strategies aimed at maintaining therapeutic efficacy while minimizing corticosteroid exposure. Recent international recommendations, including those from EULAR/ERA, advocate the use of lower glucocorticoid doses whenever feasible. Furthermore, clinical protocols employed in studies such as RITUXILUP and BLISS-LN have suggested that reduced glucocorticoid regimens may achieve favorable renal outcomes with fewer treatment-related adverse events. These findings have prompted a progressive shift toward lower steroid exposure during induction therapy.

Despite this evolving treatment paradigm, uncertainty remains regarding the optimal oral glucocorticoid dose during induction therapy for LN. The available randomized clinical trials are limited in number, differ in study design, concomitant immunosuppressive regimens, and outcome definitions, and their results have not been comprehensively synthesized. Moreover, existing reviews have generally focused on overall therapeutic strategies or specific immunosuppressive agents rather than directly comparing reduced-dose (0.5 mg/kg/day) and standard-dose (1 mg/kg/day) oral glucocorticoids as the primary intervention of interest. Consequently, clinicians continue to face uncertainty when balancing the need for rapid disease control against the risk of glucocorticoid-related toxicity, leading to variability in clinical practice.

Therefore, a systematic review of randomized controlled trials is warranted to evaluate the efficacy and safety of reduced-dose compared with standard-dose oral glucocorticoids during induction therapy in adult patients with Class III, IV, or V lupus nephritis. By synthesizing the highest-quality available evidence, this review aims to determine whether lower glucocorticoid doses provide comparable renal efficacy while reducing adverse events and infections. The findings may contribute to evidence-based clinical decision-making, support glucocorticoid-minimization strategies, and inform future clinical practice guidelines in rheumatology and nephrology.

Condition being studied Lupus nephritis (LN) is one of the most severe manifestations of systemic lupus erythematosus (SLE) and a major cause of morbidity and mortality. Approximately 40–60% of patients with SLE develop renal involvement during the course of the disease. This review will focus on adult patients (≥18 years) with biopsy-confirmed Class III, IV, or V lupus nephritis undergoing induction therapy, as these histological classes require intensive immunosuppressive treatment and are associated with a high risk of chronic kidney disease and kidney failure.

METHODS

Search strategy A comprehensive literature search was conducted in PubMed/MEDLINE, Embase and Scopus to identify relevant studies published between January 2006 and April 2026. The search was performed in April 2026, and studies published in English and Spanish were considered.

The search strategy combined controlled vocabulary (MeSH terms in PubMed and Emtree terms in Embase) with free-text terms related to the population, intervention, comparator, and study design. The main search terms included "Lupus Nephritis," "Glucocorticoids," "Prednisone," "Dose-Response Relationship, Drug," "low-dose," "high-dose," "steroid-sparing," and "Adult." Search strategies were adapted to the syntax and indexing system of each database. Reference lists of eligible studies and relevant reviews were also screened to identify additional potentially eligible studies.

Participant or population Adult patients (≥18 years) with biopsy-confirmed lupus nephritis (Class III, IV, or V according to the ISN/RPS classification) undergoing induction therapy.

Intervention Reduced-/low-dose oral glucocorticoids (approximately 0.5 mg/kg/day) administered as part of induction therapy for biopsy-confirmed Class III, IV, or V lupus nephritis in adult patients.

Comparator Standard-/high-dose oral glucocorticoids (approximately 1 mg/kg/day) administered as part of induction therapy in adult patients with biopsy-confirmed Class III, IV, or V lupus nephritis.

Study designs to be included Randomized controlled trials (RCTs).

Eligibility criteria Studies meeting the following eligibility criteria were included: (1) randomized controlled trials; (2) adult patients (≥18 years) with biopsy-confirmed Class III, IV, or V lupus nephritis; (3) direct comparison of reduced-/low-dose oral glucocorticoids (approximately 0.5 mg/kg/day) versus standard-/high-dose oral glucocorticoids (approximately 1 mg/kg/day) as part of induction therapy; and (4) studies published in English or Spanish.

Studies were excluded if they included pediatric populations (<18 years), were observational studies (cohort or case-control studies), case series, case reports, narrative reviews, systematic reviews or meta-analyses, conference abstracts without sufficient data, or studies without a comparator group.

Information sources Electronic searches were conducted in PubMed/MEDLINE, Embase and Scopus. Only studies published in English and Spanish were considered.

Main outcome(s) The primary outcome was complete renal remission at 24 weeks, as defined by each included study. Complete renal remission was assessed according to the original study definitions, which generally included normalization or near-normalization of renal function and reduction of proteinuria below the predefined threshold.

Additional outcome(s) Partial or complete renal remission at 24 weeks, renal function (serum creatinine, estimated glomerular filtration rate, proteinuria), disease activity (SLEDAI, BILAG), serological markers (anti-dsDNA, C3, C4), adverse events, serious adverse events, infections.
Mortality.
Health-related quality of life.

Data management Data from the included studies were extracted independently by two reviewers using a standardized data extraction form developed for this review. Extracted information included study characteristics, participant demographics, lupus nephritis class, intervention and comparator details, outcome definitions, efficacy outcomes, safety outcomes, and follow-up duration. Any discrepancies between reviewers were resolved through discussion and consensus.

Quality assessment / Risk of bias analysis The methodological quality and risk of bias of the included randomized controlled trials were assessed using the Cochrane Risk of Bias 2 (RoB 2) tool. The following domains were evaluated: bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported results. Each domain and the overall risk of bias were judged as "low risk of bias," "some concerns," or "high risk of bias." The assessment was performed independently by two reviewers, and any disagreements were resolved through discussion and consensus.

Strategy of data synthesis A qualitative narrative synthesis was performed. The included studies were summarized according to their study characteristics, participant demographics, intervention and comparator regimens, and reported outcomes. Efficacy outcomes (complete and partial renal remission, renal function, serological markers, and disease activity) and safety outcomes (adverse events, infections, mortality, and quality of life) were synthesized descriptively. A meta-analysis was not performed because of the limited number of eligible studies and the clinical and methodological heterogeneity in outcome definitions, glucocorticoid regimens, and study populations.

Subgroup analysis Subgroup analyses were not conducted because of the limited number of eligible studies and insufficient data to support meaningful subgroup comparisons.

Sensitivity analysis No sensitivity analyses were performed because only two randomized controlled trials met the inclusion criteria, and a quantitative meta-analysis was not conducted.

Language restriction The review was restricted to studies published in English or Spanish.

Country(ies) involved Colombia.

Other relevant information No additional relevant information.

Keywords Lupus nephritis; glucocorticoids; low-dose glucocorticoids; high-dose glucocorticoids; induction therapy.

Dissemination plans The findings of this systematic review will be disseminated through publication in a peer-reviewed scientific journal and presentation at national and international scientific conferences. The results may also contribute to future clinical practice guidelines and evidence-based decision-making in the management of lupus nephritis.

Contributions of each author

Author 1 - Gabriela Fernández Oviedo - Principal investigator. Conceived the study, developed the research protocol and PICO question, designed the search strategy, conducted the literature search, screened studies, extracted and synthesized data, interpreted the findings, and drafted the manuscript, including the discussion and conclusions.
Email: gabrielaf@uninorte.edu.co
Author 2 - Elias Forero - Content advisor. Provided expert clinical guidance on lupus nephritis, reviewed the scientific content, and critically revised the protocol and manuscript.
Email: eforero@uninorte.edu.co
Author 3 - Victor Florez - Methodological advisor. Provided methodological guidance for the systematic review, reviewed the study design and methodology, and critically revised the manuscript.
Email: vfloreza@uninorte.edu.co
Author 4 - Julieth Nieto - Co-investigator. Contributed to the literature search, study selection, data extraction, data synthesis, interpretation of the findings, and manuscript preparation, including the discussion and conclusions.
Email: juliethn@uninorte.edu.co