INPLASY PROTOCOL

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None declared.

Efficacy and safety of leflunomide combined with corticosteroids for the treatment of IgA nephropathy: a meta-analysis of randomized controlled trials

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Review question / Objective: **The efficacy and safety of leflunomide combined with corticosteroids, compared with corticosteroids alone, for the treatment of IgA nephropathy remains unknown. We performed a systematic review and meta-analysis to investigate the efficacy and safety of combined leflunomide and CS for the treatment of IgAN.**
Eligibility criteria: **Studies were included if they met the following criteria: (1) full-length articles published in English or Chinese; (2) reported as RCTs with a parallel design; (3) included adult patients with biopsy-proved IgAN; (4) patients were randomly assigned to a treatment group of a combined therapy with leflunomide and CS, and a control group with CS alone; and (5) reported at least one of the following outcomes, primary outcome: incidence of complete remission (CR) of the proteinuria, overall response (defined as CR or partial remission [PR] of proteinuria), changes of urine protein excretion (UPE, g/24h), serum creatinine (SCr), and estimated glomerular infiltrating rate (eGFR), and the incidence of adverse events, including any GI discomfort, elevated alanine aminotransferase (ALT) and/or raised aspartate aminotransferase (AST), infection, elevated glucose, and elevated BP that required medical treatment.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 March 2022 and was last updated on 28 March 2022 (registration number INPLASY202230158).

INTRODUCTION

Review question / Objective: **The efficacy and safety of leflunomide combined with corticosteroids, compared with corticosteroids alone, for the treatment of IgA nephropathy remains unknown. We performed a systematic review and meta-analysis to investigate the efficacy and safety of combined leflunomide and CS for the treatment of IgAN.**

Rationale: IgA nephropathy (IgAN) is the most common primary glomerular disease among the global population, which has become one of the important causes of end-stage renal disease (ESRD). Pathologically, autoimmune has been recognized as a major mechanism underlying the pathogenesis and progression of IgAN. Accordingly, various immunosuppressants have been suggested to be effective for preventing the deterioration of renal function and attenuation of proteinuria in patients with IgAN. Conventionally, corticosteroid (CS) is the most commonly used treatment for IgAN. Although previous stuides have shown that use of CS is associated with preserved renal function and reduced proteinuria in patients with IgAN, this treatment is associated with an increased risk of adverse events, such as gastrointestinal (GI) adverse events, infection and evaluated glucose and blood pressure (BP) etc. Besides, many immunosuppressants have been observed as alternative treatments for IgAN. Among them, leflunomide, an immunosuppressant functions as an inhibitor of pyridine synthesis, has been widely used in rheumatoid and kidney diseases in recent years. An initial randomized controlled trial (RCT) showed that leflunomide was comparable to fosinopril in reducing proteinuria in patients with IgA. However, subsequent RCTs comparing the efficacy and safety between combined treatment with leflunomide and CS with CS alone showed inconsistent results. These trials are generally of limited sample size, and a meta-analysis pooling the results of these trials is important to systematically evaluate the efficacy of combined treatment with leflunomide and CS.

Condition being studied: To evaluate the efficacy and safety of leflunomide combined with corticosteroids, compared with corticosteroids alone, for the treatment of IgA nephropathy.

METHODS

Search strategy: PubMed, Embase and the Cochrane Library (Cochrane Center Register of Controlled Trials), CNKI, and Wanfang databases until were systematically searched for relevant RCTs, using the combination of the following three groups of terms: (1) "IgA nephropathy" OR "immunoglobulin A nephropathy" OR "IgA nephritis" OR "IgA glomerulonephritis" OR "Berger's disease" OR "IgAN"; (2) "leflunomide"; and (3) "random" OR "randomly" OR "randomized" OR "randomised". The search was limited to studies in humans.

Participant or population: Adult patients with biopsy-proved IgAN.

Intervention: A treatment group of a combined therapy with leflunomide and CS.

Comparator: A control group with CS alone.

Study designs to be included: RCTs with a parallel design.

Eligibility criteria: Studies were included if they met the following criteria: (1) full-length articles published in English or Chinese; (2) reported as RCTs with a parallel design; (3) included adult patients with biopsy-proved IgAN; (4) patients were randomly assigned to a treatment group of a combined therapy with leflunomide and CS, and a control group with CS alone; and (5) reported at least one of the following outcomes, primary outcome: incidence of complete remission (CR) of the proteinuria, overall response (defined as CR or partial remission [PR] of proteinuria), changes of urine protein excretion (UPE, g/24h), serum creatinine (SCr), and estimated glomerular infiltrating rate (eGFR), and the incidence of adverse events, including any GI discomfort, elevated alanine aminotransferase (ALT) and/or raised aspartate aminotransferase (AST), infection, elevated glucose, and elevated BP that required medical treatment.

Information sources: PubMed, Embase and the Cochrane Library (Cochrane Center Register of Controlled Trials), CNKI, and Wanfang databases.

Main outcome(s): Primary outcome: incidence of complete remission (CR) of the proteinuria, overall response (defined as CR or partial remission [PR] of proteinuria), changes of urine protein excretion (UPE, g/24h), serum creatinine (SCr), and estimated glomerular infiltrating rate (eGFR), and the incidence of adverse events, including any GI discomfort, elevated alanine aminotransferase (ALT) and/or raised aspartate aminotransferase (AST), infection, elevated glucose, and elevated BP that required medical treatment.

Data management: Two authors independently performed the literature search, data extraction, and quality assessment according to inclusion criteria. Discrepancies were resolved by consensus.

Quality assessment / Risk of bias analysis: We used the seven domains of the Cochrane Risk of Bias Tool to evaluate the quality of the included studies, which include criteria concerning sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting and other potential threats to validity.

Strategy of data synthesis: Continuous variable was analyzed using mean difference (MD), whereas dichotomous data was analyzed using risk ratios (RR) with 95% confidence interval (CI). Cochrane's Q test was applied to evaluate the heterogeneity among the included studies. Also determined was the I2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. An I2 > 50% indicated significant heterogeneity among the trials. A random-effect model was used to pool the results since this model was considered to incorporate the possible between-study heterogeneity and could therefore minimize the influence of possible heterogeneity on the result.

Subgroup analysis: Predefined subgroup analyses were used to evaluate whether the results were consistent in stuides with a lower dose or the same dose of CS in the combined therapy compared to the dose of CS in controls. Potential publication bias was assessed with Egger's regression asymmetry test, or visual inspection of funnel plots if limited RCTs are included. P values were two-tailed and statistical significance was set at 0.05. We used RevMan software for the meta-analysis and statistical study (Version 5.1; Cochrane, Oxford, UK).

Sensitivity analysis: Sensitivity analysis by excluding one study at a time was also performed.

Language: English.

Country(ies) involved: China.

Other relevant information: None.

Keywords: leflunomide; corticosteroids; IgA nephropathy; randomized controlled trials; meta-analysis.

Contributions of each author:

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GL and CM conceived and designed the study. GL and CM performed database search, literature identification, data extraction, and statistical analyses. GL and CM analyzed and interpreted the results. GL drafted the manuscript. GL and CM critically revised the manuscript and approved the manuscript for submission.