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Comparative Efficacy and Safety of Therapies in IgA Nephropathy: A Network Meta-analysis of Randomized Controlled Trials

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The present study aims to compare the relative efficacy and safety of different interventions for IgA nephropathy (IgAN) with proteinuria more than 1 g/d by using network meta-analysis. We searched PubMed, Embase, and the Cochrane Library for studies compared the rate of clinical remission and/or end-stage renal disease (ESRD) and/or serious adverse events in IgAN patients with proteinuria (>1 g/d). The surface under the cumulative ranking area (SUCRA) was calculated to rank the interventions. A total of 21 randomized controlled trials with 1822 participants were included for the comparisons of 7 interventions. The rank of the most effective treatments to induce clinical remission was renin–angiotensin system inhibitors (RASi) plus urokinase, steroid plus tonsillectomy, and RASi plus steroid with a SUCRA of 0.912, 0.710, and 0.583, respectively. As for the prevention of ESRD or doubling of serum creatinine, RASi plus steroid (SUCRA 0.012) was the most effective, followed by RASi (SUCRA 0.282) and steroid (SUCRA 0.494), leaving mycophenolate mofetil as the least effective (SUCRA 0.644). There was no statistical difference among all interventions in the occurrence of serious adverse events. The current network meta-analysis demonstrated for the first time that RASi plus steroid is probably the best therapeutic choice, not only for reducing proteinuria but also for maintaining long-term renal protection.

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IgA nephropathy (IgAN) is the most prevalent immune complex related to the cause of glomerulonephritis worldwide.[1] Although the etiology and pathogenesis of IgAN are not completely understood, IgA-dominant deposition in the mesangial area has been proposed as the critical factor in the onset of IgAN.[2,3] The clinical course of IgAN is variable, and ranges from proteinuria to hematuria and even renal insufficiency. From 15% to 20% of patients with IgAN will develop end-stage renal disease (ESRD) within 10 years, and 30% to 40% within 20 years follow-up.[4] Therefore, there is a need for effective treatment strategies to reduce proteinuria and to prevent a decline in kidney function. Various treatments, expected to improve long-term renal outcomes, have been applied in IgAN patients, such as use of renin–angiotensin system inhibitors (RASi), steroids, immunosuppressive agents, urokinase, and tonsillectomy, among others.[1] Unfortunately, the optimal treatment of this common renal disease has not been identified.

The Kidney Disease Improving Global Outcomes (KDIGO) guidelines 2012 regarding IgAN suggest that patients with persistent proteinuria ≥1.0 g/d despite 3 to 6 months of intensive supportive care, and an estimated glomerular filtration rate (eGFR) >50 ml/min per 1.73 m^2, be treated with systemic glucocorticoids.[5] However, a recent retrospective analysis including 1147 patients from the European Validation Study of the Oxford Classification of IgAN (VALIGA) cohort[6] for patients with proteinuria ≥3.0 g/d demonstrated that only 4% of the individuals with supportive RASi treatment reached a level <1.0 g/d compared with 64% of those receiving corticosteroids. More recently, the Supportive versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy (STOP-IgAN)[7] and the Therapeutic Evaluation of Steroids in

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IgA Nephropathy Global (TESTING)[8] studies included IgAN patients with a broad range of proteinuria (>0.75 or 1.0 g/d) yielded an inconsistent outcome. Therefore, it is necessary to analyze the optimal therapeutic strategies for the population with proteinuria (>1 g/d).

Network meta-analysis (NMA) enables indirect comparison using a common comparator and combines direct and indirect comparisons to synchronously assess multiple treatments. In this approach, X versus Y is assessed by looking at X to Z and Y to Z.[9–11] The present study therefore aims to compare the relative efficacy and safety of different therapies for IgAN with proteinuria >1 g/d by using NMA.

Methods

Data Sources and Search Strategy

We searched PubMed, MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and the Chinese Biomedical Database for articles to 19 August 2017, without any language restriction, with key words and Medical Subject Headings that covered the following: "IgAN" or "IgA nephropathy" or "immunoglobulin A nephropathy" or "IgA nephritis" and "RASi," or "steroid" or "mycophenolate mofetil (MMF)" or "urokinase" or "tonsillectomy." We also reviewed the corresponding reference list of each retrieved article to identify any relevant studies that may be neglected. We reported the meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12]

Selection Criteria

In this meta-analysis, we collected all randomized controlled trials (RCTs) regarding comparison of therapeutic effects of different drugs in IgAN patients with proteinuria >1 g/d. Inclusion criteria for studies were as follows: (i) study population comprised patients with biopsy-proven IgAN; (ii) study design was RCT; (iii) subjects with proteinuria or 24-hour urinary protein excretion >1 g/d and renal function (eGFR ≥20 ml/min per 1.73 m^2 or serum creatinine ≤354 μmol/l (4 mg/dl), and articles provided exact data on clinical remission and/or ESRD or doubling of serum creatinine level between patients in treatment group and control group.

In this NMA, clinical remission was defined as the disappearance of urine abnormalities, proteinuria <0.3 g/d, or a decrease of proteinuria by 50% or more. The definition of ESRD was based on a serum creatinine level >707 μmol/l or 8 mg/dl or the initiation of dialysis therapy or kidney transplantation. Serious adverse events (SAEs) were defined according to the International Conference on Harmonization of Guidelines for Clinical Safety Data Management. The definition of SAEs was based on 1 of the following conditions: all-cause mortality, serious infection, gastrointestinal hemorrhage, new diabetes, fracture or osteonecrosis, and cardiovascular events.

Criteria for exclusion were as follows: (i) studies such as systemic reviews, comments, case reports, conference abstracts, and editorials; (ii) articles that had no definitions on clinical remission or renal function; and (iii) subjects with mild or severe proteinuria, or pathology confirmed as crescent.

Included trials reported comparisons of 7 interventions (placebo, RASi, steroid, MMF, steroid + RASi, RASi + urokinase, and tonsillectomy combined with steroid pulse therapy [TSP]). Supportive and immunosuppressive interventions were classified according to the type of drugs, monotherapy or combination, regardless of dose. NMA integrates data from direct comparisons of treatments within trials and from indirect comparisons of interventions assessed against a common comparator in separate trials to compare all investigated treatments.

Data Extraction and Quality Assessment

Two authors (PY and HZ) abstracted data and quality assessment independently into an electronic database. The investigators cross-checked the data and reached consensus for any discrepancies through discussion. Disagreements were settled through discussions or referral to a third author (GX). All potentially eligible citations that we had searched were examined in detail to identify studies that satisfied our criteria. Reference lists of identified trials and review articles were manually scanned to identify related research references at the same time (Figure 1).

The extracted data included name of first author, year of publication, kidney function, proteinuria, sample size, doses and modalities of treatment, control, follow-up duration, steroid doses and modalities of treatment, number of patients receiving control treatment/condition, and outcome of proteinuria or kidney function.

The RCT quality assessment was completed by using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) risk of bias tool including selection, performance, detection, attrition, reporting, and other bias.

Risk of Bias Assessment

Two authors (PY and HZ) independently assessed the methodological quality of included trials using a slightly adapted version of the risk of bias approach of the Cochrane Collaboration. The publication bias assessment was performed via Deek funnel plot asymmetry.

Statistical Analysis

Data were abstracted and analyzed by R software (version 3.3.2, R Foundation for Statistical Computing,