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The efficacy and safety of immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome: a network meta-analysis

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Citation

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Review question

The efficacy and safety of different immunosuppressive treatments for idiopathic membranous nephropathy is still controversial. So, a network meta-analysis will be perfomed to compare different immunosuppressive treatments in IMN.

Searches

PubMed, EMBASE, Cochrane Library, Web of Science,Clinical trials, Sinomed, CNKI, WANFANG DATA, VIP were searched for randomized controlled trials reporting the treatments for IMN to Feburary 1, 2018.

Types of study to be included

Randomized controlled trials (RCTs)

Condition or domain being studied

Idiopathic membranous nephropathy (IMN) remains one of the most common causes of nephrotic syndrome in adults. Because of the clinical features and prognosis of IMN are variable, the disease with a high rate of spontaneous remission. Studies have shown that spontaneous complete remission of proteinuria is observed after a variable period of time (4 to 120 months) in approximately 30% to 40% of adult patients. Despite this, 10% to 30% of patients progresses toward end-stage kidney disease (ESKD) within 10 years. If follow-up is extended to 10 to 20 years, progression to ESKD may occur in 50% to 60% of patients without treatment. Immunosuppression is supposed to induce disease remission and reduce the risk of progression to ESRD or death. The treatment of IMN mainly include conservative treatment and immunosuppressive therapy. Supportive therapy with angiotensin converting-enzyme inhibitors (ACE inhibitors) or angiotensin-receptor blockers (ARBs), a diet low in salt and protein, and statins are initiated in all patients for 6 months. Given the slowly progressive natural course and substantial spontaneous remission rate of this disorder, immunosuppressive agents are recommended for patients who are developing complications of nephrotic syndrome or at high risk of disease progression. Although various immunosuppressive agents have been used for treatment of idiopathic MN, their use remains controversial. The numbers of corresponding studies related to tacrolimus, mycophenolate mofetil, adrenocorticotropic hormone, azathioprine, mizoribine, and Tripterygium wilfordii are still too sparse to draw final conclusions.

Participants/population

IMN in adults with nephrotic syndrome.

Intervention(s), exposure(s)

Various immunosuppressive agents for the treatment of IMN, including adrenocorticotropic hormone, azathioprine, chlorambucil, cyclophosphamide, cyclosporine, leflunomide, Mycophenolate mofetil, mizoribine, rituximab, tacrolimus, Tripterygium wilfordii.

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Comparator(s)/control
Different immunosuppressive agents or supportive therapy.

Context

Primary outcome(s)
Total remission (TR). It was defined as either Complete remission (CR) or partial remission (PR). Complete and partial remission of nephrotic syndrome was assessed according to the definition provided in each single study. In the absence of an explicit definition, CR was defined as proteinuria less than 0.3 g/24 h and with a normal or stable SCr (within 50% of baseline value). In the absence of an explicit definition, PR was defined as proteinuria reduced by at least 50% and remained between 0.3-3.5g/24h with a normal or stable SCr (within 50% of baseline value).

Timing and effect measures

Secondary outcome(s)
Include 24h UTP, Scr and relapse.

Timing and effect measures

Data extraction (selection and coding)
Two independent reviewers will screen the literatures and extract data separately. The basic information in the literatures was included according to the “Data Extraction Form” of the study, including the name, author, year of publication, source, source of cases and country of the article, multi-center or not and the total number of cases, the number of patients, age and course of disease in experimental and control groups, intervening measure and controlled method, outcome index and adverse effect, etc. The literatures will be arranged in accordance with the code of intervening measures. The extracted data will be entered into a standardized Excel file (Microsoft Corporation). Where details of the included studies are inadequate to allow accurate grouping, authors will be contacted for more detail.

Risk of bias (quality) assessment
We will assess the risk of bias as “low risk”, “unclear risk” or “high risk”, in accordance with the Cochrane Collaboration’s Risk of bias tool as described in the Cochrane Hand book for Systematic Reviews of Interventions. The assessment details include: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting and other sources of bias. Two independent review authors (HFX and XTL) will assess the risk of bias in selected studies. Degree of agreement between the two independent raters will be reported. Any disagreements will be resolved by a third review author (YGF or HSY). Where necessary, the authors of the studies will be contacted for further information. Studies will be classified as having high risk of bias if two or more domains were rated as high risk of bias; low if five or more were rated as low risk of bias and none was rated as high risk of bias, and all other cases will be assumed to pertain to moderate risk.

For each outcome, we will assess the quality of the evidence of the NMA results using an adapted version of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. We produce a “summary of findings table” for each clinical recommendation outcome. The quality of evidence will be classified by the GRADE group into four levels: high quality, moderate quality, low quality and very low quality. This process will be performed using GRADE pro V.3.6 software (http://www.gradeworkinggroup.org/).

Strategy for data synthesis
NMA combines direct and indirect evidence for all relative treatment effects and provides estimates with maximum power. We will summarize characteristics of the included RCTs and present direct and indirect comparisons between different acupuncture therapies.

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Pairwise meta-analysis

We will do a traditional pairwise meta-analysis, which is used for consistency check and an evaluation of heterogeneity, for all available direct evidence comparing two treatments using R V.3.5 software (https://cran.r-project.org/src/base/R-3/). The I^2 statistic will be applied to quantify the extent of between-trial heterogeneity, with I^2 >50% indicating considerable heterogeneity. The random-effects model will be used as the main model. Furthermore, the results of the random-effects model will be compared with that of the fixed-effect model to test the stability of the results. Risk ratio (RR) with 95% confidence interval (CI) will be calculated for a dichotomous variable. Mean difference (MD) with 95% CI will be estimated for a continuous outcome.

Network meta-analysis
A random-effects network meta-analysis within a frequency framework will be performed. MD and RR for each outcome with 95%CI was summarized. We will estimate the ranking probabilities for all treatments of being at each possible rank for each intervention. The treatment hierarchy will be summarized and reported as surface under the cumulative ranking curve (SUCRA) and mean ranks. SUCRA is a percentage interpreted as the probability of a treatment is the most effective without uncertainty on the outcome, which is equal to 1 when the treatment is certain to be the best and 0 when it is certain to be the worst. To check the assumption of consistency in the entire analytical network, a design-by-treatment approach will be used. A loop-specific approach will be used to evaluate the presence of inconsistency locally in each closed loop. The node splitting method and heatmap will be used to assess the inconsistency of the model with separating evidence on a particular comparison into direct and indirect evidence. A global heterogeneity will be assessed with I^2-statistic and predictive interval plot that incorporate the extent of heterogeneity will be used to evaluate the extent of uncertainty in the estimated effect size locally. Uncertainty affected by heterogeneity will be defined as disagreement between the confidence intervals of relative treatment effects and their predictive intervals. The transitivity assumption underlying network meta-analysis will be evaluated by comparing the distribution of clinical variables which could act as effect modifiers across treatment comparisons. Contribution plot will be used to assess the contribution of each direct comparison to the estimation of each network meta-analytic summary effect, since it is helpful to evaluate the overall quality of evidence from network meta-analysis. Additionally, a comparison-adjusted funnel plot will be used to detect the potential publication bias in the results between small and large studies. To assess whether the results will be impacted by study characteristics (effect modifiers), subgroup analysis was conducted. Univariate and multivariate meta-regression will be further conducted to control the confounding factors. Besides, sensitivity analysis of network meta-analysis will be conducted to validate the robustness of the results. All analyses will be conducted using R 3.5.0 (network meta-analysis, assessment of global heterogeneity and SUCRA graphs), and STATA 13.0 (pairwise meta-analysis, estimation of inconsistency, transitivity and local heterogeneity, funnel plot).

Analysis of subgroups or subsets

Study duration (<12 months, 12-24 months, ?24 months); Recruitment of participants (Asian, Non-Asian); Center (Single center , Multicenter).

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Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Versions
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