INPLASY PROTOCOL

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The authors have no conflicts of interest to disclose.

Comparison efficacy and safety of biologics targeting interleukin pathways in patients with ankylosing spondylitis: a protocol for systematic review and Bayesian network meta-analysis of randomized controlled trials

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Review question / Objective: **Recently, the emergence of interleukin inhibitors has changed the treatment landscape of ankylosing spondylitis (AS). Although this previous evidence suggests that IL inhibitor share similar clinical efficacy in patients with AS, there are many IL inhibitor (such as IL-6, IL-12, IL-17 and IL-23 inhibitor) that are currently being used to treat AS. However, there is no published evidence comparing the efficacy and safety of these various IL inhibitors in patients with AS.**
Information sources: **Electronic database PubMed, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials will be systematically searched from inception to December 2020. Reference lists of included articles were searched for additional records. The search terms used in the database include ankylosing spondylitis, spondylarthritis, anti-interleukin agents, interleukin inhibitor, interleukin blockers, IL inhibitors, IL-6, IL-17, IL-23, IL-12, Random, Randomized, Control, RCTs, Clinical trial. Moreover, we will try to contact the correspondent authors via e-mail to obtain the missing data.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 February 2021 and was last updated on 28 February 2021 (registration number INPLASY202120081).

INTRODUCTION

Review question / Objective: **Recently, the emergence of interleukin inhibitors has changed the treatment landscape of ankylosing spondylitis (AS). Although this previous evidence suggests that IL inhibitor share similar clinical efficacy in patients with AS, there are many IL inhibitor (such as IL-6, IL-12, IL-17 and IL-23 inhibitor) that are currently being used to treat AS. However, there is no published evidence**

comparing the efficacy and safety of these various IL inhibitors in patients with AS.

Condition being studied: AS is a chronic inflammatory disease that mainly affects the medial joints and their accessory ligaments, but also peripheral joints, such as the sacroiliac joints. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used as the basic treatment for ankylosing spondylitis, and there are patients with refractory ankylosing spondylitis who have been treated with NSAIDs for more than 6 months without relief. Recently, the emergence of interleukin inhibitors has changed the treatment landscape of AS. Although this previous evidence suggests that IL inhibitor share similar clinical efficacy in patients with AS, there are many IL inhibitor (such as IL-6, IL-12, IL-17 and IL-23 inhibitor) that are currently being used to treat AS. However, there is no published evidence comparing the efficacy and safety of these various IL inhibitors in patients with AS. Pairwise meta-analyses could not solve these clinical questions, because few RCTs have directly compared different types of IL inhibitors in patients with AS. Hence, we undertook this systematic review and network meta-analysis of RCTs to comprehensively compare and rank different types of IL inhibitors for AS.

METHODS

Search strategy: The search terms used in the database include ankylosing spondylitis, spondylarthritis, anti-interleukin agents, interleukin inhibitor, interleukin blockers, IL inhibitors, IL-6, IL-17, IL-23, IL-12, Random, Randomized, Control, RCTs, Clinical trial.Electronic database PubMed, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials will be systematically searched from inception to December 2020. Reference lists of included articles were searched for additional records.

Participant or population: Participants who meet the diagnostic criteria of the modified New York criteria in 1984 will be included, and there are no restrictions on the gender, race, age, or education.

Intervention: The intervention method of the experiment group will include any kinds of interleukin inhibitor, including IL-6, IL-12, IL-17 and IL-23 inhibitor. In addition, we also include interleukin inhibitor in combination with another drug interleukin inhibitor.

Comparator: Placebo and/or other interleukin inhibitor will be selected as the control interventions.

Study designs to be included: This systematic review and Bayesian network meta-analysis will include all randomized clinical trials (RCTs) that using interleukin inhibitor for AS and regardless of the sample size, publication status. Non-RCTs, animal trials, or case report will be excluded. The language will be restricted in English.

Eligibility criteria: Type of participant. Participants who meet the diagnostic criteria of the modified New York criteria in 1984 will be included, and there are no restrictions on the gender, race, age, or education Type of interventions. The intervention method of the experiment group will include any kinds of interleukin inhibitor, including IL-6, IL-12, IL-17 and IL-23 inhibitor. In addition, we also include interleukin inhibitor in combination with another drug interleukin inhibitor. Placebo and/or other interleukin inhibitor will be selected as the control interventions. Type of outcomes Primary outcomes. The primary outcome of the study includes Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Assessment of Spondylarthritis International Society response criteria (ASAS). 2.3.3.2. Secondary outcomes. The secondary outcomes will include ankylosing spondylitis quality of life (ASQoL), high-sensitivity C-reactive protein, and adverse events (such as treatment-emergent adverse events, discontinuation due to any adverse event, infections, death) Study design. This systematic review and Bayesian network meta-analysis will

include all randomized clinical trials (RCTs) that using interleukin inhibitor for AS and regardless of the sample size, publication status. Non-RCTs, animal trials, or case report will be excluded. The language will be restricted in English. Search strategy Electronic database PubMed, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials will be systematically searched from inception to December 2020. Reference lists of included articles were searched for additional records.

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Main outcome(s): Primary outcomes. The primary outcome of the study includes Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Assessment of Spondylarthritis International Society response criteria (ASAS). Secondary outcomes. The secondary outcomes will include ankylosing spondylitis quality of life (ASQoL), high-sensitivity C-reactive protein, and adverse events (such as treatment-emergent adverse events, discontinuation due to any adverse event, infections, death).

Quality assessment / Risk of bias analysis: Two authors will independently assess the risk of bias of included studies using a modified version of the Cochrane Collaboration's Risk-of Bias Tool, which include random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Each domain was classified as low-risk, unclear-risk, high-risk of bias as appropriate. Any disagreements will be resolved through consensus with the third investigators (GZ).

Strategy of data synthesis: Pairwise meta-analyses were performed with a DerSimonian and Laird random effects model to calculate the pooled estimates of mean differences (MDs) with 95% CI or odds ratios (ORs) with 95% CI of direct comparisons between control group and experiment group using STATA 14.2. We assessed statistical heterogeneity in each pairwise comparison with the I^2 statistic and p value. We used the funnel plot and Egger's test to detect publication bias, if at least ten studies were available. Second, the network meta-analyses were performed with a Bayesian hierarchical random effects model using OpenBUGS. For each comparison, a mean effect estimate with its 95% credible interval (CrI) was calculated using the Markov chains Monte Carlo method. Two Markov chains were run simultaneously with different arbitrarily chosen initial values. Inconsistency between direct and indirect sources of evidence was statistically assessed globally (by comparison of the fit and parsimony of consistency and inconsistency models) and locally (by calculation of the difference between direct and indirect estimates in all closed loops in the network). The node splitting method was used to calculate the inconsistency of the model, which separated evidence on a comparison into direct and indirect evidence. The treatment hierarchy was summarized and reported as surface under the cumulative ranking curve (SUCRA). We also plotted a comparison-adjusted funnel plot for the network meta-analysis, to detect the presence of any dominant publication bias in network meta-analysis. Effect modifier analyses were performed to detect potential sources of clinical and methodologic heterogeneity within each network meta-analysis.

Subgroup analysis: If necessary, subgroup analyses will be done for both pairwise

meta-analyses and network meta-analysis according to different types of drug, stage of disease, study quality.

Sensitivity analysis: To ensure robustness of the results, sensitivity analyses will be performed to effect of each study on the random effects model. If there is no significant change in the results, the results are stable.

Language: The language will be restricted in English.

Country(ies) involved: China.

Keywords: interleukin inhibitors, ankylosing spondylitis, network meta-analysis, efficacy.

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