INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Traditional Chinese medicine formulations for treating ankylosing spondylitis: A protocol for systematic review and network meta-analysis

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Review question / Objective: **Ankylosing spondylitis (AS) is a major public health problem worldwide that causes chronic disability and imposes a huge burden on healthcare and the economy. Efficacious, safe, and inexpensive drugs for AS treatment are not available. Numerous clinical studies have shown that traditional Chinese medicine (TCM) formulations for AS treatment have high efficacy and high safety. However, because of the diversity of TCM formulations, their efficacy and safety are controversial. Therefore, we will undertake a systematic review and network meta-analysis to evaluate the efficacy and safety of various TCM formulations for AS.**
Information sources **PubMed, Cochrane Library, Embase, China National Knowledge Infrastructure, Web of Science, Wanfang Database, Chinese Scientific Journal Database, and Chinese BiomedicalDatabase, Chinese Clinical Registry and International Clinical Trials Registry Platform.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 April 2022 and was last updated on 25 April 2022 (registration number INPLASY202240147).

INTRODUCTION

Review question / Objective: **Ankylosing spondylitis (AS) is a major public health problem worldwide that causes chronic disability and imposes a huge burden on healthcare and the economy. Efficacious, safe, and inexpensive drugs for AS treatment are not available. Numerous clinical studies have shown that traditional Chinese medicine (TCM) formulations for AS treatment have high efficacy and high safety. However, because of the diversity of TCM formulations, their efficacy and safety are controversial. Therefore, we will undertake a systematic review and network**

meta-analysis to evaluate the efficacy and safety of various TCM formulations for AS.

Condition being studied: AS is a common chronic inflammatory rheumatic disease characterized by an insidious onset, a long course, and a high prevalence of disability. AS has become a major public health issue worldwide. The exact pathogenesis of AS is not known, but evidence suggests that it is closely related to genetic and environmental factors. Symptomatic treatment is available for patients with AS, but a practical way to prevent or cure AS is not available. The potential benefits of complementary medicine and alternative medicine have been receiving increasing interest recently because of the absence of treatment options. Treatment based on TCM theory has been used for AS. Recent studies of the effects of TCM formulations based on RCTs have, in general, demonstrated their efficacy. However, as the number of RCTs of TCM-based treatment for AS has increased, clinical decision-making has become increasingly difficult. Most studies have focused on the efficacy of a single type of TCM formulation, leading to an absence of direct comparisons between different TCM formulations and uncertainty about which TCM formulation will provide the greatest benefit to patients with AS.

METHODS

Participant or population: Participants aged >18 years diagnosed with AS according to modified New York criteria regardless of nationality, sex, ethnicity, disease severity, and disease duration, among others.

Intervention: The experimental group will receive a TCM formulation or TCM formulation combined with routine pharmacotherapy (Western medicine). The nature of the TCM formulation will not be limited to a decoction, Chinese patent medicine, pill, or capsule.

Comparator: Routine pharmacotherapy (Western medicine) or a placebo.

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

Eligibility criteria: RCTs that assess the efficacy and safety of TCM formulations for AS treatment will be included. The language of the studies will be limited to Chinese or English.Descriptive studies, conference abstracts, clinical experiences, case reports, letters, protocols, reviews, and animal studies will be excluded. For duplicated studies, we will also select the most informative and complete reports.Types of participants: This protocol will include participants aged >18 years diagnosed with AS according to modified New York criteria regardless of nationality, sex, ethnicity, disease severity, and disease duration, among others.Type of interventions and comparisons:The experimental group will receive a TCM formulation or TCM rmulation combined with routine pharmacotherapy (Western medicine). Thfoe nature of the TCM formulation will not be limited to a decoction, Chinese patent medicine, pill, or capsule. The control group will have received routine pharmacotherapy (Western medicine) or a placebo. We will also exclude studies in which ≥2 TCM formulations have been combined to treat AS.Types of outcomes: The primary outcome will include the Bath Ankylosing Spondylitis Disease Activity Index, Bath Ankylosing Spondylitis Function Index, visual analog scale, and total effective rate. The Bath Ankylosing Spondylitis Metrology Index, inflammation markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and adverse events will be selected as the secondary outcome. We will retrieve relevant RCTs from the inception date to March 2022 by electronic and manual means.

Information sources: PubMed, Cochrane Library, Embase, China National Knowledge Infrastructure, Web of Science, Wanfang Database, Chinese Scientific Journal Database, and Chinese BiomedicalDatabase, Chinese Clinical Registry and International Clinical Trials Registry Platform.

Main outcome(s): Bath Ankylosing Spondylitis Disease Activity Index, Bath Ankylosing Spondylitis Function Index, visual analogue scale, and total effective rate.

Additional outcome(s): The Bath Ankylosing Spondylitis Metrology Index, inflammation markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and adverse events.

Quality assessment / Risk of bias analysis: The tool proffered by the Cochrane Collaboration will be used to assess the risk of bias for individual studies. The evaluation criteria are selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Each domain will be classified as having a "high", "low", or "unclear" risk of bias as appropriate. If necessary, differences will be resolved by further discussion in consultation with a third reviewer.

Strategy of data synthesis: We will use STATA 15.0 (www.stata.com/) for paired meta-analysis. For dichotomous variables, results will be expressed as odds ratios with 95% confidence intervals (CI). For continuous variables, the mean difference or standardized mean difference with the 95%CI will be calculated. Heterogeneity across trials will be assessed with the I2 statistic.If I2 <50%, we will select the fixed-effects model; otherwise, the random-effects model will be used. We will undertake an NMA based on a Markov chain Monte Carlo approach to compare the effects of various TCM formulations. A random-effects model will be used to deal with heterogeneity between studies because this is considered to be the most conservative method. Convergence of iterations will be assessed using Brooks–Gelman–Rubin plots, and the potential scale reduction factor (PSRF) employed to indicate convergence, with PSRF tending to 1 representing better convergence. To assess the inconsistency between direct evidence and indirect evidence, we will use the nodal-splitting method. The efficacy of various TCM formulations will be ranked according to the surface under the cumulative ranking curve (SUCRA). The SUCRA curve will be expressed as a percentage, with the best treatment being 100% and the worst being 0%. Data analysis will be done using Addis 1.16.8 (http://drugis.org/software/addis/), WinBUGS 1.4.39 (www.mrc-bsu.cam.ac.uk/software/bugs/the-bugs-project-winbugs/), and STATA 16.0.

Subgroup analysis: A subgroup analysis will be carried out if significant clinical heterogeneity between studies (I2 >50%). We will analyse the subgroup of patients according to the sample size, different types of control group, treatment duration, follow-up duration, different TCM formulations, and other relevant parameters to explore the impact of these factors on results. Only a descriptive analysis will be undertaken if there is no clear source of heterogeneity.

Sensitivity analysis: Sensitivity analyses will be conducted to explore the stability of the results. By removing each study individually, the impact of each study on the overall effect will be assessed.

Country(ies) involved: China.

Keywords: traditional Chinese medicine formulation; ankylosing spondylitis; network meta-analyses; protocol.

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