

Clinical application of Ganshuang granule in treatment of liver fibrosis: a protocol for developing an expert consensus

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Background: Liver fibrosis (LF) is a common liver disease in humans, which can progress to cirrhosis and increase the risk of liver failure and hepatocellular carcinoma. Ganshuang granule (GSG) has been used in the treatment of various chronic liver diseases and has demonstrated antifibrotic activity. However, there is no expert consensus (EC) involving the clinical application of GSG for the treatment of LF that has been reported. Therefore, we plan to develop an EC based on strict procedures.

Methods: The EC will be developed according to (I) Discussion on Issues Related to Clinical Experts Consensus of Chinese Patent Medicine, (II) Methods of Developing and Revising Expert Panel Consensus on Chinese Patent Medical Clinical Application and (III) The Reporting Standards for Expert Consensus on the Use of Chinese Patient Medicines in Clinical Practice (made by the China Association of Chinese Medicine). We will set up a Consensus Project Group, which constructs clinical questions to take into account population, intervention, comparison, and outcomes (PICO). Then search and evaluate the eligible literature. The draft recommendations will be developed using the Nominal Group Technique (NGT) after evidence syntheses. In formulating EC, we will also take into account the results of peer reviews and declarations of interests. We will take the protocol as a roadmap to systematically develop evidence for the clinical application of GSG in the treatment of LF.

Discussion: This will be the first EC developed for the clinical application of GSG in the treatment of LF, which will improve the clinical medication standards, and provide scientific and rational prescription medication guidance for clinicians engaged in the diagnosis and treatment of liver-related diseases.

Trial registration: The present EC has been registered on the International Practice Guidelines Registry Platform (<http://www.guidelines-registry.org/>), with registration number IPGRP-2019CN020.

Keywords: Liver fibrosis (LF); Ganshuang granule (GSG); clinical practice expert consensus (EC); protocol

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Introduction

Liver fibrosis (LF) is a type of pathophysiological process, which refers to the abnormal hyperplasia of intrahepatic connective tissue caused by chronic liver injury during a long-term wound-healing response. It can be caused by various pathogenic factors. There are many etiologies of LF such as viral hepatitis, alcoholic liver, fatty liver, autoimmune diseases, and so on. Liver injuries undergo LF when repairing and healing, which without timely and effective treatment, will progress to cirrhosis and increase the risk of liver failure and hepatocellular carcinoma (1).

China is a high epidemic area for hepatitis B virus (HBV) infection. According to statistics, about 120 million people in China are hepatitis B surface antigen (HBsAg) positive and 30 million people suffering from chronic hepatitis B due to untimely treatment after infection with HBV (1). In patients with chronic hepatitis B, the compensatory period (LF) of cirrhosis has an incidence of more than 90%. The annual incidence of decompensated cirrhosis is about 3%, and the cumulative incidence of 5 years is about 16% (2,3). As well, the incidence of alcoholic liver, fatty liver, and drug-induced hepatitis also increased significantly. In China alone, about 300 million people are affected by liver disease, which has a major impact on the global burden of liver disease (4).

LF can further develop into liver cirrhosis and has reversible potential due to its own ability to regenerate and gradually absorb scar tissue. Therefore, many scholars have so far believed that LF and early cirrhosis can be reversed (5), and it is stand in need of developing anti-fibrotic therapies that can prevent, halt, or even reverse LF or cirrhosis. Compared with synthetic medicines, traditional Chinese medicine (TCM) has attracted widespread attention as an alternative clinical therapy because of its effective and extensive treatment efficacy with a lower incidence of side effects and great prospect in clinical practice (6). TCM supplies abundant resources for the development of anti-inflammatory, anti-infectious, and anti-fibrotic drug candidates. In some cases, TCM is effective involving advanced LF and liver cirrhosis (7).

Ganshuang granule (GSG) is based on a prescription from traditional Chinese medicine and has been used in the treatment of various chronic liver diseases. TCM theory holds that GSG has the functions of protecting the liver, strengthening the spleen, clearing heat and stasis, as well as softening and resolving hard mass. GSG was introduced in the Interpretation of Clinical Diagnosis and Treatment Guidelines of Traditional Chinese Medicine: Liver and

Gallbladder Disease Volume (8) and the Interpretation of Clinical Pathway—The Digestive Diseases Volume (9). GSG has been widely used in clinical institutions of various provinces and cities in China since it was listed in the market. It has since been confirmed (10-15) that GSG has efficacy when treating acute and chronic hepatitis, LF, and liver cirrhosis, with a good safety profile. Studies have demonstrated that this may occur due to GSG suppressing the activation of hepatic stellate cells (HSCs), thus producing an antifibrotic effect (14,16,17). GSG has significant effects on relieving the symptoms of liver pain, fatigue, abdominal distension, and greasy weariness. The granule dosage form has little stimulation to the stomach, which is especially suitable for patients with cirrhosis of the liver accompanied by varicose veins in the lower segment of the gastric fundus esophagus. This can significantly reduce the risk of bleeding. Particularly in the absence of Western medicine for the treatment of LF and cirrhosis, GSG provides a safe and effective possibility for treatment. However, there is no expert consensus (EC) involving the clinical application of GSG for the treatment of LF that has been reported.

With the accumulation of basic research, evidence-based medicine, and clinical application experiences, in order to provide guidance for the safe and rational drug use in LF and cirrhosis treatment in clinical practice. We will develop an EC for the clinical application of GSG in the treatment of LF. This consensus will improve the clinical medication standards, which will include aspects such as clinically applicable conditions, usage, dosage, drug withdrawal principle, adverse reactions, and clinical drug contraindications.

Methods

Principle

We will refer to the Discussion on Issues Related to Clinical Experts Consensus of Chinese Patent Medicine and the Methods of Developing and Revising Expert Panel Consensus on Chinese Patent Medical Clinical Application of China Association of Chinese Medicine (CACM) (18,19) to formulate our EC. We will also follow the Reporting Standards for Expert Consensus on the Use of Chinese Patient Medicines in Clinical Practice Made by CACM for writing (20). We have registered the EC on the International Practice Guidelines Registry Platform, and the registration number is IPGRP-2019CN020.

Guideline development institutions, target users and population

The EC was launched by the Society of Liver Diseases, CACM, and has been applied for approval by CACM. The consensus will be published as a group standard. The target users of the EC are doctors specializing in liver diseases, digestion, and other related areas in hospitals of all levels. Relevant nurses and pharmacists can also refer to them. The target populations are patients with acute and chronic hepatitis, LF, or cirrhosis.

Consensus project group

The Consensus Project Group has two subgroups: Expert Groups and Working Groups. The Expert Group includes clinical experts, methodologist experts, and pharmaceutical experts. The Working Group includes secretaries and personnel from pharmaceutical enterprises. The establishment of the Expert Group should fully consider the balanced distribution of its members in terms of disciplines, specialties, and regions, so as to ensure that the composition of the Expert Group is fully representative. The following principles should be adhered to for the Expert Group: (I) more than 30 persons with senior titles, (II) methodologists account for at least 10%, and pharmacists for at least 5%, and (III) everyone is required to sign a declaration of conflict of interest. After the establishment of the Expert Group, one clinical expert should be designated as the group leader and one methodological expert as the deputy group leader.

The following items will be the assignment of the Consensus Expert Group: (I) to identify clinical questions, (II) to identify the protocol of the EC, (III) to complete the systematic review and the grade of the evidence to form the decision tables, (IV) to handle the opinions of external auditors, and (V) to write the full text of the EC and submit it to the steering committee for review.

The assignment of the Consensus Working Group will be as follows: (I) to investigate clinical questions, (II) to draft the protocol of the EC, (III) to complete the external audit work of the EC, (IV) to document the complete establishing process of the EC in detail and (V) to coordinate related issues.

Declaration of interests and funding support

All members of this consensus have signed a statement of conflict of interest. This stated that there was no commercial, professional or other interests related to

the subject of this consensus, as well as all interests that may have been affected by the outcome of this consensus. The conflict of interest and its handling strategy will be summarized and reported in the final consensus document.

Formulating key questions

Constructing clinical questions in the form of PICO

Constructing clinical questions through questionnaires, the respondents are required to meet the following conditions. Respondents should have more than 100 clinicians familiar with GSG (including clinical experts in the Expert Groups), with the professional title of principal doctor or above. As well, no more than 2 persons should come from the same department in the same hospital. Also taken into account is the geographical hospital location, hospital level, and doctors of both traditional Chinese medicine and Western medicine, amongst other factors.

Selection and evaluation of outcome indicators

Based on preliminary literature analysis and previous clinical experience, the following outcomes are taken into consideration in the process of formulating this consensus: (I) disease progression, (II) histopathological results, (III) endpoint events, (IV) clinical symptoms, (V) serological markers, and (VI) adverse events. Serological markers include hyaluronic acid (HA), type III procollagen peptide including its metabolic fragments (PIIIP, PIINP, PIIICP), type IV collagen including its metabolic fragments (PIV-NP, PIVNC1, PIV) and laminin (LN). All of these outcomes can represent the efficacy of treatment for HF.

The Consensus Expert Group is responsible for organizing clinical experts to make the list of outcomes, categorize, and rank them uniformly. These are then judged according to the Visual Analogue Scale (VAS): 1–3 will be considered not important, 4–6 important, and 7–9 critical.

Evidence retrieval and synthesis

Searching existing systematic reviews and evaluating their relevance

The consensus-formulating group will search the Cochrane Library, Medline, and Embase to obtain systematic reviews related to the topics of the consensus.

Determination of the searching strategy

After developing a detailed search strategy, we will

systematically search the literature from inception to July 31st, 2019 in the Cochrane Library, Medline, Embase, Chinese Biomedical Literature Database (Sinomed), Chinese National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), and the Wanfang Data Knowledge Service Platform.

We will also search the clinical trial registration platform (such as Clinical Trails), the international consensus registration platform (<http://www.guideline-registry.cn>), Chinese clinical consensus library (<http://cgc-chinaebm.org>) and other domestic and foreign clinical trial registries and consensus libraries.

In addition, we will manually search textbooks, important periodicals, academic conference papers, published standardized documents, and monographs.

Free words and MeSH terms including “Ganshuang Keli”, “Ganshuang granule”, “Ganshuang particles”, “Liver Fibroses”, “Liver Fibrosis”, “Liver Cirrhosis”, and “hepatitis B”.

Literature selection and evidence syntheses

The Expert Group is responsible for literature selection and evidence syntheses including original studies, systematic reviews, and meta-analysis. The research results will be comprehensively collated according to the determined P (patient or population), I (intervention), C (comparison), and O (outcome). Then a detailed search strategy will be formulated with inclusion criteria and exclusion criteria. Systematic reviews with high quality developed in the last two years will be applied directly. Otherwise, it will be considered whether there are any new related original studies published after the publication of the systematic reviews. If there are new original studies published and the results of these studies changed from the previous review, we will update the systematic review. If there is no available systematic review or the quality of the systematic review is very low, then it is advised a new systematic review should be performed.

Evidence assessment

We will evaluate the evidence quality based on the recommendations of GRADE guideline and classify the evidence into either high, moderate, low, and very low (21). Randomized controlled trials (RCTs) are regarded as high-quality evidence, while observational studies are considered to be low-quality evidence. The evidence of each study will be evaluated based on the results. The methodologists will be responsible for assessing the quality, drafting summaries

of the evidence, and submitting them to the Consensus Development Group meeting. Through this step, we will form a summary table and a comprehensive report of the evidence.

Developing recommendations or suggestions

Upon accomplishing the GRADE evidence profile, the Consensus Working Group will draft preliminary recommendations based on quality, overall benefits, patients' values, patients' preferences, and health economics. The Consensus Working Group developed the draft recommendations using the Nominal Group Technique (NGT) to organize the arguments and suggestions for clinical questions (both those that are supported by evidence and those that are not).

Process of NGT

- (I) All necessary documentations are prepared including drug instructions, clinical research reports, evidence synthesis reports, evidence summary forms, and the ballot lists of recommendations or suggestions for this process.
- (II) The Consensus Working Group contacts experts and coordinates the time to ensure maximum attendance. This requires experts to attend more than 50%, in which clinical experts must vote, while experts in other fields can choose whether to vote or not according to their wishes.
- (III) Experts meetings are convened, ballot lists of recommendations and suggestions are distributed, and all the documents above are prepared by the Consensus Working Group.
- (IV) For items supported by evidence or not, each member fills in the “Recommendation Voting Form” and the “Consensus Proposal Voting Form” independently.
- (V) After counting the votes, the experts will elaborate opinions on the items that don't reach consensus. The Consensus Working Group will summarize these opinions and make appropriate modifications to the description of the consensus items. The vote is then held again.
- (VI) After a maximum of 3 rounds of voting, all items are listed in the decision table. The items with a consensus are marked with recommendation/suggestion strength, while the items without consensus are marked “no consensus”.

Rules for consensus-building

Each recommendation item in the questionnaire will use 5 choices including A: strong recommendation, B: weak recommendation, C: unclear recommendation, D: weak no recommendation, and E: strong no recommendation. For each item, a consensus can be reached if more than 50% of the experts vote on any option other than “C”, the direction and strength of the recommendation are determined directly. If the total votes of “A” and “B” or “D” and “E” exceed 70%, a consensus will be reached to determine the recommendation direction, and the recommendation strength is considered “weak”. Under any other circumstances in the voting, it will be deemed that no consensus has been reached, and the consensus recommendation will enter into the next round of voting (not exceeding 3 rounds).

The rules for consensus on the experts’ suggestions are as follows: three choices of A: recommendation, B: neutrality, and C: no recommendation. These rules will apply to each recommendation item in the questionnaire. If the total votes of “A” or “C” exceed 50%, a consensus can be reached. In other cases, it is deemed that no consensus has been reached, and the consensus for suggestions will enter the next round of voting (again should not exceed 3 rounds).

Peer review of consensus

Considering the practical applications of the consensus, it will be submitted for peer review by external experts including those in the fields of traditional Chinese medicine and western medicine. The Consensus Development Group will record the review process and collect the proposals from reviewers, and strengths are revised if necessary. Finally, the peer review reports and consensus submissions are formed upon the results of the review.

Reporting publication and updating of the consensus

The consensus is to eventually be drafted and reported according to the format recommended by the Essential Reporting Items for Practice Guidelines in Healthcare (RIGHT) Working Group (22). Meanwhile, the consensus will be drafted according to the reporting framework formulated by the Consensus Steering Group and the rules stipulated by the group standards of CACM. The consensus will be officially released and published by the authoritative

organization CACM, published in relevant journals.

We will initiate a consensus update process when new relevant evidence emerges and the evidence changes have an impact on consensus recommendations. The update cycle is between 2–5 years. These updates will be in accordance with the current international consensus update report specification: CheckUp (23).

Promotion, implementation, and evaluation of the consensus

After publishing, we will promote the consensus following basic principles. It will be promoted in the following ways: (I) the consensus will be presented at professional academic conferences and thematic training, (II) popularize the contents of EC through medical journals publishing and book publishing, and (III) online publishing EC, disseminating consensus through the network.

Discussion

This will be the first EC developed for the clinical application of GSG in the treatment of LF based on strict procedures, which will improve the clinical medication standards, and provide scientific and rational prescription medication guidance for clinicians engaged in the diagnosis and treatment of liver-related diseases.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://>

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