Author's response to reviews

Title: Efficacy and safety of Qing-Feng-Gan-Ke Granules in patients with postinfectious cough: study protocol of a novel-design phase 3 placebo-controlled, double-blind randomized trial

Authors:

Wei Liu (lovekk_cool@126.com)
Hongli Jiang (81489337@qq.com)
Ruiming Zhang (zhruim-001@163.com)
Bing Mao (maobing2013@yeah.net)
Faguang Jin (jinfag@fmmu.edu.cn)
Liangji Liu (llj6505@163.com)
Youyu Long (longyou@eyou.com)
Liying Cui (cuiliying306@hotmail.com)
Suyun Li (lisuyun2000@yahoo.com.cn)
Yunqing Zhong (jackvictor666666@163.com)

Version: 4 Date: 5 July 2015

Author's response to reviews: see over
Dear Prof. Tom Rowles,
Firstly, thank you for giving me this great chance to revise my paper. Secondly, I will giving a point-by-point response to the comments from dear Dr. Anne Elizabeth Vertigan.

1. **Could the authors please elaborate on the four diagnostic methods (inspection, auscultation, enquiry, pulse-taking etc).**

I am so glad that you are interested in TCM. Here I would give you a detailed explanation about the four diagnostic methods—the methods to observe and diagnose diseases.

The four diagnostic methods, namely inspection, auscultation and olfaction, inquiry, and pulse-taking and palpation, refer to the four basic procedures used in diagnosing a disease. They are the presuppositions of correct differentiation and effective treatment in TCM.

When a disease occurs, there must be its abnormal outward manifestations from which the pathological changes may be inferred, as is stated by a great TCM doctor in Qing Dynasty, "To want knowing the internal conditions of the body, the external manifestations of the body should be observed; to diagnose the external parts of the body may also know the internal conditions. That is because the internal conditions of the body are always reflected on the exterior of the body". The four diagnostic methods examine and learn about the pathological conditions from different angle and aspect and find out the etiology and pathogenesis, thereby providing the basis for SDT (Syndrome Differentiation and Treatment). The four methods are related to and supplement one another. They cannot be separated from one another, each having its specific function that cannot be substituted. In clinical practice, only when the four techniques are organically combined can a disease be understood all-sidedly. Thus, a correct diagnosis can be made.

**Inspection**

Inspection is the first diagnostic procedure by which the physician may observe the patient's vitality, complexion, physical build, head, neck, five sense organs, skin, tongue, external genitalia and anus on purpose so as to understand the condition of a disease. TCM holds that the human body is an organic whole. The exterior of the body is closely related to the internal organs. Take observation the vitality and complexion for examples, the vitality refers to the general external manifestations of life activity of the human body, including spirit, consciousness and thinking. And it is the outward sign of the conditions of Qi and blood, Yin and Yang, or the organs. The vitality is manifested in manifold aspects, such as eyesight, complexion, facial expressions, physical build, behavior and so on, among which the
expression of the eyes is the most important. This is because "all the vital essence from the organs converges into the eyes." From the observation of vitality the physician may infer the abundance or inadequacy of the vital essence, analyze mildness or the severeness of the disease and predict the prognosis of disease. It is quite evident that the observation of vitality is of an important significance in diagnosing a disease. The manifestations of vitality are as follows; being of vitality, pseudo-vitality, and loss of vitality.

The observation of complexion is a diagnostic method for inspecting the colour and lustre of the face. TCM divides the facial colours into blue, yellow, red, pale and black, also known as the "five colours", whose changes may indicates the nature and the location of a disease. Generally speaking, red complexion indicates heat syndromes; white complexion indicates cold and deficiency syndrome; yellow complexion deficiency and dampness syndromes; blue complexion suggests pain and cold syndrome, blood stasis and convulsion; and black complexion hints deficiency of the kidney, blood stasis and fluid retention. Inspection also includes observation of the physical build. By the observation of sturdiness, weakness, obesity or emaciation as well as the posture of the movement and stillness, different kinds of diseases may be found out. And, in particular, the observation of the tongue is a unique procedure in TCM diagnosis. It is used to observe the changes of the tongue proper and the tongue coating so as to determine the abundance or decline of vital qi, tell the location of a disease, distinguish the nature of pathogenic factors and infer the degree of seriousness of a disease.

**Auscultation and Olfaction**

Another diagnostic method is auscultation and olfaction. Auscultation means listening to the patient's voice, speaking, respiration, coughing and moaning. By auscultation, the doctor can not only learn about the changes of the phonatory organ, but also infer the pathological changes of the internal organs. While olfaction means smelling the patient's odor of the secretion and excretion. By and large, stench odor usually indicates heat syndromes of excess; stinking odor suggests cold syndromes of deficiency; and foul and sour odor implies retention of food.

**Inquiry**

This is a diagnostic method in which the patient or his companion are inquired to collect the information concerning a disease. The content of inquiry includes the chief complaints, present case history past history, life history, family history, as well as age, sex, native place, occupation, address and so forth inquiry, though covering a wide range of topics, should be conducted step by step in a planned way, with questions focused on the chief complaint and the history of present disease. Therefore, when asking a
patient, the physician should focus his attention on the chief complaint to understand both the main reasons for the disease and clearest, the most suffered symptoms of the patient. Besides, the physician should understand the occurrence, progress, diagnosis and treatment of a disease through asking. Here is an outline of inquiring about the present illness:

A. Asking about Chills and Fever
B. Asking about Perspiration   This is a procedure for the physician to differentiate the conditions of interior and exterior, heat and cold, deficiency and excess of a disease. Asking about perspiration includes the presence of sweating, the location of sweating, the time of sweating and the amount of sweating.
C. Asking about Diet and Appetite   Asking diet and appetite may know the conditions of the spleen and stomach. It includes: thirst and drinking appetite and amount of food taste.
D. Asking about Defecation and Urination   This is also a procedure in which the physician may learn whether the digestion and absorption as well as fluid metabolism are normal or not, and also learn about frequency, time, amount, quality, color, odor of defecation and urination and accompanied syndromes.
E. Questioning about Pain   Asking about nature of the pain helps tell the cause and pathogenesis; asking about locality of the pain helps understand pathological changes of internal organs and meridians.
F. Questioning about Sleep   It refers to inquiring about insomnia, dreaminess and lethargy to know excess and deficiency of Yin and Yang.

Pulse-taking and Palpation
It is the fourth diagnostic method, including pulse-taking and, on the other, palpation of different parts of the body. The former is a diagnostic procedure by which the physician may feel the patient's radial arteries with the finger-tips to judge pulse condition, thus learning and inferring the condition of illness. The latter is also a procedure by which the physician may touch, feel, push and press certain parts of the body to detect local abnormal changes, thereby determining the location and nature of the disease.

The location for feeling the pulse at present time is the patient's "cunkou". Cunkou refers to obvious pulsative place of the radial artery on both sides of the wrist, and is divided into three regions: cun, guan and chi, which, on the left hand, reflect respectively the conditions of the heart, liver and kidney and, on the right hand, the conditions of the lung, the spleen, the stomach and the kidney. TCM holds that each of the six regions for pulse-feeling corresponds to one of the internal organs and reveals the
pathologic changes of the relevant organ. For this reason, cunkou pulse-taking is commonly accepted by practitioners through the ages and still used today. The pulse is differentiated in terms of depth (superficial or deep), speed (rapid or slow), strength (forceful or weak), shape (thick or thready, soft or hard) and rhythm. Different pulse conditions indicate different syndromes. For example, superficial pulse, which is easily felt with gentle touch, indicates exterior syndromes and is present at the early stage of exogenous diseases; while deep pulse, which is felt only by heavy pressure, indicates interior syndromes, and so on.

Palpation may be conducted in three procedures: touching, stroking and pressing. Touching is used to feel a certain part of the body, like the forehead or limbs with the fingers of palms, thereby detecting the body temperature, dampness or dryness; stroking refers to examining the patient's some parts of the body with the hands, e.g., a swelling, to learn the shape, size and sensation of the swelling; pressing means pushing and pressing over some parts of the body with the hands, e.g., the chest or abdomen, to make sure if they are tenderness, or have any cakings when pressed.

Inspection, auscultation and olfaction, inquiry and pulse-taking and palpation are the four diagnostic methods to understand the pathological conditions. They can not be separated, but are related to and complement one another. In clinical practice only by combining the four can a comprehensive and systematic understanding of the condition of a disease be gained, thereby, making a correct diagnosis.

2. Further elaboration is required on the side effects of other medications? what was the severity and prevalence of these side effects?
I have to say that the side effects I listed in the manuscript are the most common ones that happen in the clinical application of these medications(not only in the application in treating PIC). Therefore, the rate at which these side effects occur develops at different rates for different effects. There is a lack of published literature reporting these medications in the treatment of PIC because of the poor effect. Therefore, no information about the severity and prevalence of these side effects of these medications in treatment of PIC could not be provided. In the Background part, just the basic background information are needed(these western medications indeed result in side effects).I really hope you could understand.

3. Could the authors please re-word the phrase “contributing to resultful conclusions that laid a solid foundation for the current phase III trial”?
I changed the sentence to “To the best of our knowledge, the phase II study was the first well-designed placebo-controlled clinical trial that reported
TCM as a remedy for PIC, and its resultful conclusions provide foundations for the current phase III trial.”

4. **Limitations of the study should be addressed in the discussion.**
The limitations of this study have already been addressed in the Discussion part, the last paragraph of the main manuscript.

“Several limitations and drawbacks of this study are as follows. Firstly, since we are going to conduct different intervention durations in the two parts, some patients with relatively mild cough would be treated for 14 days while those with relatively severe cough will be treated for 10 days, which is paradoxical and against common clinical practice. Secondly, although a careful knowledge of medical history and physical examination including serologic tests may provide clues to diagnosis, the diagnosis of PIC still largely depends on clinical exclusion[5]. Therefore, the possibility of misdiagnosis cannot be ruled out. Thirdly, an objective cough measurement is not included in this study. Many video and sound recording surveillance have been used in clinic to objectively monitor the cough frequency and severity[36-39]. However some studies reported a poor relationship between cough frequency and cough symptom score[37-39]. Moreover, although operating a manual recording instrument is easy for patients, it requires a good compliance. Otherwise, considerable errors could be induced. In addition, how to effectively and sensitively distinguish and filter the external vocal interference, and also record the weak electromyographic signals of pulmonary muscles are still the technical bottlenecks for the development of 24h cough monitors. Furthermore, the expensive cost also limits the use of cough recording surveillance. For the above reasons, objective cough measurements are not included in our study. Fourthly, the lack of data from old people over the age of 65 fails to provide information about the efficacy and safety of QFGKG in this group of patients.”

5. **The upper age limit is not consistent with many treatment studies of cough.**
I have to admit that we did not include the old people (>65Y). This is a limitation of our study. I added this limitation in the Discussion part. But we have reasons to support our decision. This clinical study was designed and conducted strictly follow the China GCP(Good Clinical Practice) guideline. It suggests that, normally, age range of subjects who are included in the clinical new drug trials (II, III, IV) should be from 18 to 65 (of course, the age range could be modified by trial designers as the circumstances may require). We chose this age range after a comprehensive consideration (compliance, safety, ethic, data integrity and validity, etc.) I can not provide you the original guideline because these information was
written in the printed copy and there is no electronic version. I could give you some examples:

6. The numbering and labeling of tables and figures is still not clear.
I have explicitly and precisely numbered and labelled the tables and figures. Each table and figure has been numbered and cited in sequence using Arabic numerals in consecutive numerical order.
I think the reason why you think the tables and figures are not numbered and labelled clearly is because of the format of the automatically generated PDF. According to the “Instructions for authors”, smaller tables are required to be pasted into the end of the document text file while larger ones too wide for a portrait page and all the figures are required to be uploaded separately as additional files. But additional files will not be displayed in the final, laid-out PDF of the article, but only a link will be provided to the files.

Best wishes,
Wei Liu