Section 1

07

Clinical Trials

From Zheng Classification to New Drug Discovery in Chinese Medicine

China

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Summary

Rheumatoid arthritis (RA) was adopted as a disease model to examine how Zheng classification, based on disease diagnosis, represents a novel approach to the research and development of combinational drugs design based on *Fu Fang* (a Chinese herbal formula). Some unique research design and methods were introduced.

Background and Justification

Zheng classification, the core of traditional Chinese medicine (TCM) theory, promotes personalized medicine by modifying the clinical diagnosis into a more precise aggregate when integrating Zheng classification with disease diagnosis. The advantages of this aggregation can contribute to the discovery of new drugs.

Description

In TCM theory, Zheng, also termed "syndrome" or "pattern", is the basic unit and a key concept. Zheng can be understood as a guideline for patient classification in clinical practice from a different viewpoint or dimension when compared with disease diagnosis in biomedicine. Over the past 30 years, an increasing number of researchers have focused their attention on developing evidence for Zheng and sought to identify its mechanism. As of August 2015, there were 711,299 papers on Zheng in Chinese lodged in the China National Knowledge Infrastructure (CNKI) together with 843 papers on the PubMed database. New trends are emerging in Zheng research in the integration of Zheng classification with biomedical disease diagnosis (Jiang *et al.*, 2012).

Zheng classification can provide deeper insight into the specific indications of drugs

The most important influence when blending Zheng classification and clinical diagnosis in biomedicine is the improvement of clinical diagnosis (Lu *et al.*, 2012; Jiang *et al.*, 2012).

Zheng classification uses phenotype-like clinical manifestations to classify patients, thus further assisting in their stratification for intervention to improve the efficacy of the treatment based on a Zheng classification-related clinical trial strategy.

A previous study showed that patients with rheumatoid arthritis (RA) 'cold' Zheng had a significantly higher response rate to the biomedical therapy than 'hot' Zheng patients with RA (He *et al*., 2007; He *et al.*, 2008). The differences between the two Zheng have been outlines (Lu *et al.*, 2012a; Lu *et al.*, 2012b). Consequently, it was hypothesized that a comparison analysis between the responsive and non-responsive cases might help detect

the effectiveness-related signs and symptoms, after which a further round of clinical trials could be conducted, focusing on the patient subgroup with positively related signs and symptoms as part of inclusion criteria. It could therefore be anticipated that a higher effective rate would be obtained in the second round of clinical trials as the patients would have been stratified further in relation to their response-related factors. Early in 2015, a two-stage clinical trial of TCM therapy (*Tripterygium wilfordii* polyglycoside tablets and *Yi Shen Juan Bi* pills) for the management of RA was published (Jiang *et al.*, 2015). The stage one trial was an open-label trial and aimed to explore which groups of TCM information correlate with better efficacy whilst the stage two trial was a randomized, controlled, double-blind trial that incorporated the efficacy-related information identified in the stage-one trial into the inclusion criteria. The results conclusively demonstrated the role of Zheng classification in efficacy improvement.

This innovative clinical trial design can also be used for the clinical efficacy evaluation of an "old" drug to "renew" its indication (Zhang *et al.*, 2014). Moreover, the Zheng classification concept may also assist with the assessment of drug safety. A 2013 study provides a new paradigm for better understanding the risks and limitations when using potentially toxic herbs in clinical applications (Tan *et al.*, 2013).

The incorporation of the Zheng classification into biomedical disease diagnosis will lead to a new era in the development of personalized medicine, very much a trend for the future, involving medication tailored to individual patients and incorporating the use of multiple therapeutic agents and the assessment of nutritional, psychological and lifestyle factors when deciding the best course of treatment. These early investigations suggest that Zheng classification could be of use in moving forward with improving clinical diagnosis improvement, and provide momentum for the move towards therapeutics and pharmacology. Improving treatment efficacy with specific therapeutic indications may identify specific indications that provide research opportunities for the development of new drugs.

Zheng classification used to help choose a single appropriate drug for a range of diseases

Another important concept in TCM, termed "Treating Different Diseases with the Same Therapy" (TDDST) has been applied in practice. Some patients with RA and others with coronary heart disease (CHD) can be treated with similar therapies (e.g. activation of blood stasis for RA patients with a Zheng of blood stasis). This suggests that there might be some connection between the conditions of RA and CHD in line with a TCM diagnosis within the context of an imbalance in bodily functions, biological networks or biological bases. In order to substantiate such concepts, there exists a need to track down

any interlinking data from reliable databases (Zhang *et al.*, 2011). Our study proposed a hierarchical analysis algorithm termed "discrete derivatives" based on the frequencies of concurrent Medical Subject Headings (MeSH) terms, providing some significant results which support the concept of TDDST, together with the biological markers and biological networks existing in RA and CHD (Zhang *et al.*, 2014). These networks can be affected by herbs widely used in TCM therapies for both RA and CHD (Niu *et al.*, 2014). Another example to is to explore commonalities in different diseases using mass spectrometry-based metabolic phenotyping studies to identify any generalized metabolic defects associated with arthritis, together with the metabolic signatures of four major types of arthritis (Bi Zheng in CM): RA, osteoarthritis, ankylosing spondylitis, and gout (Jiang *et al.*, 2013). A global metabolic profile has been identified for all arthritic patients, suggesting that there are common metabolic defects resulting from joint inflammation and lesion. Meanwhile, differentially expressed serum metabolites have been identified, constituting a unique metabolic signature for each type of arthritis that can be used as biomarkers for diagnosis and patient stratification. Similar symptoms shared by the different types of arthritis have continued to confound clinical diagnoses and represent a clinical dilemma when deciding treatment choices with a more personalized or generalized approach. Therefore, Zheng classification, as an approach to identifying relevant diseases in patients within different Zheng categories can certainly contribute important concepts in the innovation of treatments for different diseases with the same drug and this concept offers a broad vision for improving drug discovery.

Zheng classification offers a clue to the development of combination therapeutics

The paradigm shift in new drug discovery is via the modulation of multiple proteins rather than a single target. Some successful drugs now in the marketplace have, by chance, wound up hitting several targets, which is perhaps why they are effective. Active Chinese herbal ingredients and thousands of traditional herbal formulae have long been viewed as a rich source of therapeutic leads in drug discovery. Combinatory drugs or health products focus on multi-target drugs and this has emerged as a new paradigm in drug discovery. Therefore, the intention of our research was to purposefully aim at multiple targets with a combination of drugs. Taking new drug discovery in rheumatology as an example, we reported results from text mining and mapped the biological network of RA and integrated it into a Cytoscape network (Zheng *et al.*, 2011). We established a comprehensive platform covering a large number of public molecular databases including SinoMed, PubMed, TCMD, DrugBank, ChEMBL, GAD, GO, IntAct and PharmGKB. The state-of-the-art use of protein structure, protein–protein interaction, signalling, genetic interaction, metabolic networks and chemical similarity in the discovery of drug targets was summarized. The prediction method consisted of two main steps: (i) prediction of

the pharmacological effects from chemical structures of 100 compound combinations (from text-mining results), and (ii) the inference of unknown combination drug-target interactions based on the similarity of their pharmacological effects. Ten combination drug candidates were finally arrived at. Experimental and clinical validations are now necessary, but the originality of the method lies in the prediction of their potential pharmacological similarity for any combination drug candidates and in the integration of the available chemical, proteomic, genomic and pharmacological data within a unified framework. We anticipate that this type of data might streamline the re-targeting of drugs.

Partnerships

Among the partners of the various projects were the China Academy of Chinese Medical Sciences, Shanghai Jiao Tong University Affiliated Sixth People's Hospital and the China Astronaut Research and Training Centre.

Impact

Among the awards won by the research team was a one-year studentship provided by the Mr. Kwok Yat Wai and Madam Kwok Chung Bo Fun Graduate School Development Fund to C. Liang in 2015.

The special circumstances: Institute for Advancing Translational Medicine in Bone & Joint Diseases provide multidisciplinary scientists from Faculty of Science and School of Chinese Medicine a synergistic collaboration platform which efficiently and effectively translate basic scientific findings into knowledge that benefits patients with bone and joint diseases, which is often described as an effort to carry scientific knowledge 'from bench to bedside'.

Replicability

Two patients have been awarded for the team's products, while another four patent applications were under consideration.

Lessons Learned

In the past few years, the pharmacy industry has seen a shift from the search for 'magic bullets' that specifically target a single disease-causing molecule towards the pursuit

of combination therapies that comprise more than one active ingredient. While some researchers have focused on studying combinations of conventional drugs, others, with good reason, have turned to Chinese herbal medicines.

Future Plans

Zheng classification shows great promise for outlining drug indications that may have important benefits from both a patient and an economic perspective. Moreover, the goal of using old drugs in new ways is becoming more efficient through the use of a Zheng classification approach. To accelerate intelligent drug discovery, we propose combination drug strategies in which the new drugs target illnesses on the Zheng disease classification subnetworks. Nevertheless, the emergence of validated Zheng classification applications looks ever more certain, bringing with it the hope of a new therapeutic era.

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