Traditional Chinese Medicine in the Treatment of Influenza

China

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Total cost: USD 471,275

Summary

First noted in Mexico in 2009, the highly-damaging influenza A (H1N1) spread rapidly to other regions of the world. Effective and low-cost medicine was urgently needed, but in short supply in China. Traditional Chinese Medicine (TCM) has been used to treat seasonal influenza for thousands of years. During the early days of the 2009 H1N1 pandemic, the herbal formula Maxingshigan-Yinqiaosan (MY) was used widely by TCM practitioners to reduce symptoms but with no exact clinical evidence with regard to its efficacy. Supported by the Beijing Municipal Science and Technology Commission and the Beijing Administration of Traditional Chinese Medicine, during the H1N1 epidemic we conducted a prospective, randomized, controlled, non-blinded, multicentre trial that ran between July and November 2009 at 11 sites in four Chinese provinces.

Registered on the most authoritative website, ClinicalTrials.gov, the study used standard, strict modern evidence-based methods. 410 participants were randomly assigned to a control group, an oseltamelvir (Tamiflu™) group, an MY group and an oseltamivir plus MY group. Patients were prescribed following the principle of same symptom, same disease, same regimen, and same dose.

Oseltamivir and MY, both alone and in combination, reduced time to fever resolution in patients with H1N1 suggesting MY may represent an alternative H1N1 treatment. No side effects were observed.

This is the first research to study the efficacy and safety of TCM in the treatment of H1N1 using modern assessment methods with results published in the internationally-renowned *Annals of Internal Medicine*. The methods used were accorded a high ranking and the study was listed by five international authoritative medical databases, signifying that TCM treatment for H1N1 had won international recognition.

Background and Justification

In April 2009, cases of human infection with H1N1 influenza A virus were identified in the United States and Mexico and spread rapidly to other regions of the world, resulting in the first influenza pandemic since 1968. By March 2010 almost all countries had reported cases, and more than 17,700 deaths among laboratory-confirmed cases had been reported to the World Health Organization (WHO).

The antiviral agent oseltamivir (Tamiflu™) was widely used during the H1N1 influenza A pandemic, as recommended by the WHO. No direct comparative evidence on the role of oseltamivir in the H1N1 influenza A pandemic was reported, but isolates of pandemic H1N1 influenza A virus with resistance to oseltamivir were detected.

During that period, oseltamivir was expensive and the supply was insufficient. Thus, cheaper alternative drugs to oseltamivir were urgently needed.

Traditional Chinese Medicine (TCM) has been used to treat seasonal influenza for thousands of years. In a meta-analysis of 31 randomized clinical trials including 5,514 cases of influenza, the authors concluded that TCM had significantly increased clinical efficacy compared with placebo or no intervention (93.46% vs. 79.03%, respectively; $P<0.001$), and no serious adverse effects were reported.

Modern pharmacological studies have demonstrated that some TCM formulae have antiviral and immunomodulating effects. During the early days of the 2009 H1N1 influenza A pandemic, the popular herbal formula Maxingshigan-Yinqiaosan (MY) was used widely by TCM practitioners to reduce symptoms.

Here we report on a prospective, randomized, controlled, non-blinded, multicentre trial carried out during the H1N1 influenza A epidemic between July and November 2009 at 11 medical sites in four provinces in China.

Patient enrolment

Patients aged 15 to 70 years who presented within 72 hours of onset of H1N1 influenza A symptoms were enrolled in the trial. All patients (410) were admitted to hospitals where they could be quarantined and observed. Patients who fulfilled all of the following criteria were included: documented body temperature 37.5°C or greater; one or more respiratory symptoms (cough, sore throat or rhinorrhea); and a positive result for H1N1 influenza A virus via a real-time reverse transcriptase polymerase chain reaction (RT-PCR). Patients were excluded if they had received an influenza vaccination in the 12 months before the start of the study; had active, clinically significant chronic illness or HIV/AIDS; were receiving systemic steroids or other immunosuppressants; had taken Chinese medicinal herbs or antiviral drugs; were pregnant; or had new infiltrate of the lungs on chest radiography.

Drug administration

The TCM formula used was Maxingshigan-Yinqiaosan (MY), which is composed of 12 herbs. The criteria for the quality of the herbs used were in accordance with the 2005 Chinese pharmacopoeia. Herbs from the same source were distributed to the 11 study sites. Before the start of the trial, the herbs were tested for heavy metals, microbial contamination and residual pesticides, and all results met Chinese safety standards.

The 12 herbs formula included: zhimahuang (honey-fried Herba Ephedrae), 6g; zhimu (Rhizoma Anemarrhenae), 10g; qinghao (Herba Artemisiae Annuae), 15g; shigao (Gypsum Fibrosum), 30g; yin-hua (Flos Lonicerae Japonicae), 15g; huangqin (Radix Scutellariae),

15g; chaoxingren (stir-baked Semen Armeniacae Amarum), 15g; lianqiao (Fructus Forsythiae), 15g; bohe (Fructus Forsythiae), 6g; zhebeimu (Bulbus Fritillariae Thunbergii), 10g; niubangzi (Fructus Arctii Tosum), 15g; and gancao (Radix Et Rhizoma Glycyrrhizae), 10g.

At each study site, a trained technician prepared the decoction according to a standardized procedure; each unit of formula yielded 800ml of decoction. Oseltamivir was given as capsules, and the TCM intervention was given as a decoction. Placebo capsules were not used; the control group received no intervention.

After agreeing to participate, signing the informed consent form and completing the baseline visit, all patients were randomly assigned to one of the three active treatment groups or the control group by using random-number tables. Randomization was stratified by the four study centres, located in Beijing, Yantai, Chengdu and Wuhan. These centres were selected to ensure broad geographic spread and representation of H1N1 influenza A epidemic areas in mainland China. A statistician who was not involved in data collection or analysis produced the randomization list. A coordinator at each site who was blinded to the participants' characteristics assigned the participants to treatment by telephoning a contact at the study-coordinating centre in Beijing Chao-Yang Hospital. The contact was not involved in the number generation and recruitment process. Participants were then randomly allocated to the control group or one of the intervention groups: oral oseltamivir, 75mg daily for 5 days; MY decoction, 200ml orally 4 times daily for 5 days, or oseltamivir plus MY.

All participants were hospitalized so that they could be quarantined and closely observed and were followed until discharge. Adherence to therapy was assessed by nurses who were blinded to the study. On the basis of the attending physician's judgment, participants were allowed to use acetaminophen if their body temperature was greater than 39°C. Likewise, the need for antibiotics was determined by the attending physicians. Any use of acetaminophen or antibiotics was recorded on the case record forms.

Assessment

During hospitalization, nurses who were blinded to the study measured participants' body temperatures daily at 02:00-06:00, 06:00-10:00, 10:00-14:00, 14:00-18:00, 18:00-22:00 and 22:00-02:00. The presence and severity of influenza symptoms (cough, sore throat, rhinorrhoea, headache and fatigue) and drug-associated side effects were also recorded daily. Symptom scores (0 = absent, 1 = mild, 2 = moderate, and 3 = severe) were recorded and compared with baseline scores until five days after treatment in all groups.

The primary efficacy end-point was designated as the time from randomization to fever resolution. Secondary outcomes were the proportion of patients who became afebrile,

improvement in symptom scores during the study period, side effects associated with the interventions, and incidence of secondary complications of influenza such as otitis, bronchitis, sinusitis or pneumonia.

Throat swab specimens were collected from all participants and sent to local branches of the Chinese Centre for Disease Control and Prevention for H1N1 influenza A RNA testing by using the protocol from the US Centres for Disease Control and Prevention. Serial real-time RT-PCR for viral RNA titres was performed daily from enrolment until discharge.

Full details of the numbers of patients involved and the steps undertaken during the study are presented in Fig. 1.

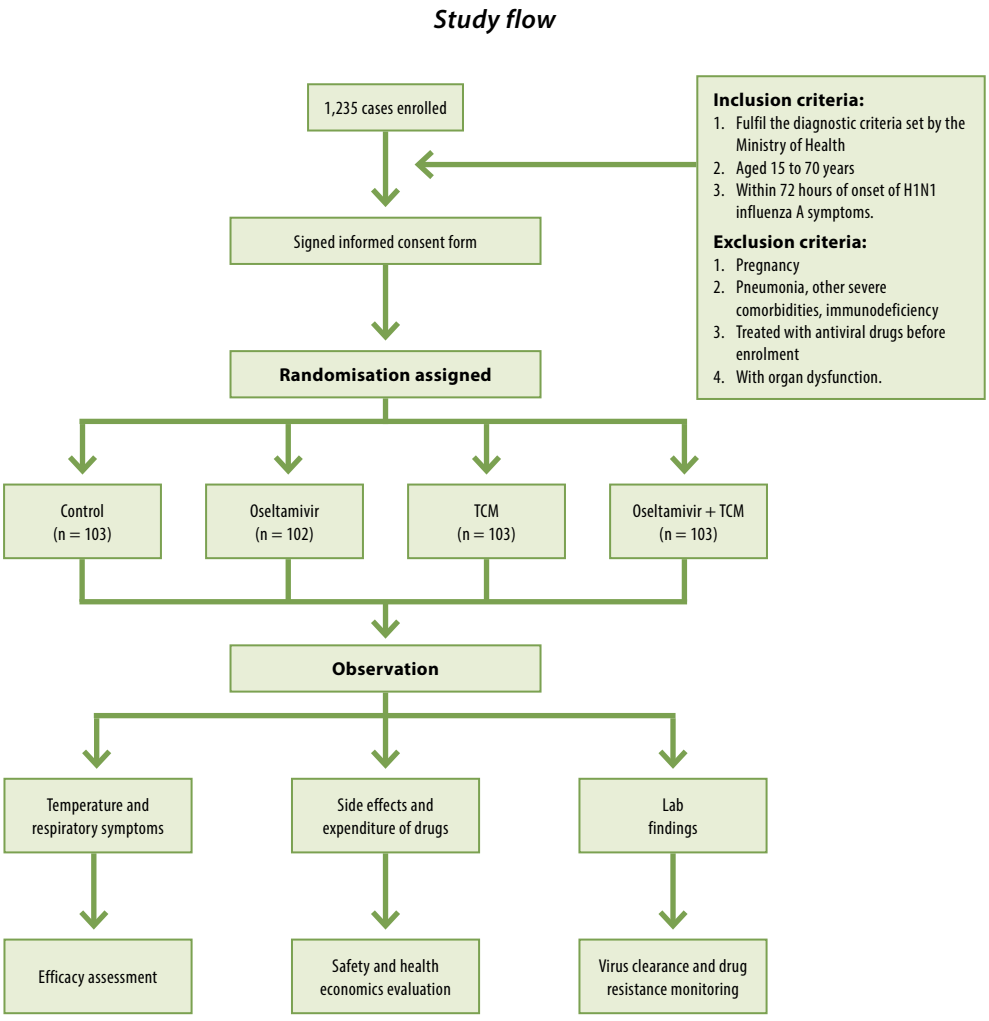

Figure 1: The study flow protocol assigning participants to the various drug and treatment regimes and their subsequent management.

Baseline characteristics did not differ among the 4 groups

Characteristic	Control Group (n = 103)	Oseltamivir Group (n = 102)	MY Group (n = 103)	Oseltamivir Plus MY Group (n = 102)
Men, n (%)	58 (56.3)	58 (57.8)	65 (63.1)	52 (51.0)
Mean age (SD), y	18.7 (5.3)	19.0 (6.2)	19.6 (7.1)	19.2 (6.5)
Received vaccine, n (%)	2 (2.0)	2 (2.0)	0 (0.0)	2 (2.1)
Comorbid conditions, n (%)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Temperature, n (%)				
37.5–38.0 °C	28 (27.2)	26 (25.5)	22 (21.4)	24 (23.5)
38.1–39.0 °C	60 (58.3)	52 (51.0)	59 (57.3)	53 (52.0)
>39.0 °C	15 (14.6)	24 (23.5)	22 (21.4)	25 (24.5)
Median symptom score (IQR)*	3.0 (2.0–3.0)	3.0 (2.0–3.0)	3.0 (2.0–3.0)	3.0 (2.0–3.0)
Symptom, n (%)				
Cough	78 (75.7)	75 (73.5)	76 (73.8)	73 (71.6)
Sore throat	66 (64.1)	57 (55.9)	61 (59.2)	63 (61.8)
Rhinorrhea	19 (18.4)	25 (24.5)	25 (24.3)	23 (22.5)
Headache	45 (43.7)	46 (45.1)	40 (38.8)	47 (46.1)
Fatigue	43 (41.7)	36 (35.3)	33 (32.4)	41 (40.2)
Median leukocyte count (IQR), × 10^9 cells/L	5.8 (4.6–6.8)	5.7 (4.4–6.9)	5.1 (4.0–6.3)	5.5 (4.5–7.3)
Median interval between onset of illness and randomization (IQR), h	30.0 (11.0–47.0)	35 (17–40)	35 (25–49)	32 (16–53)
Days hospitalized				
Median (IQR)	6 (5–7)	6 (5–7)	6 (5–7)	6 (5–7)
Range	4–14	3–13	3–11	2–11

Characteristics:

- young, rare comorbidities and three-quarters of the participants with temperature above 38 ℃
- interval between onset of illness and enrollment between 30 and 35 hrs

Table 1: Patients' baseline characteristics with the primary and secondary outcomes of the measures undertaken. (SD = standard deviation; IQR = interquartile range).

Participant characteristics

410 participants aged 15 to 69 years from 11 sites were included in the trial. Of the 410 participants, 102, 103, and 102 were randomly assigned to receive oseltamivir, MY, and combination therapy, respectively, while the remainder were assigned to a control group (Fig. 1). Baseline demographic characteristics, clinical features and laboratory findings were similar among the four groups (Table 1). Three-quarters of the patients had temperatures above 38°C, co-morbidities were rare (one person), and most patients were younger than 20 years old. The interval between onset of illness and enrolment in the study was between 30 and 35 hours.

Virological outcomes

Both baseline swab specimens and specimens collected on days 1 to 5 for evaluation of virus shedding were available for 148 of the 410 participants.

Changes in virus shedding from baseline to day 5 did not differ by treatment group (p=0.69 for time-by-treatment interaction).

However, oseltamir and MY, both alone and in combination, reduced time to fever resolution in patients with H1N1, compared to controls. These results suggest that MY may represent an alternative treatment for H1N1 infections (Table 2).

Fever duration (hr)				
Kaplan-Meier Estimate	Control Group (n=103)	Oseltamivir Group (n=102)	MY Group (n=103)	Oseltamivir Plus MY Group (n=102)
Median time to alleviation of fever (95% CI), h	26.0 (24.0 to 33.0)	20.0 (17.0 to 24.0)	16.0 (14.0 to 17.0)	15.0 (12.0 to 18.0)
Difference in median time to fever resolution (95% CI), %* Relative to control group	-	-34 (-46 to -20); P<0.001	- 37 (-49 to -23); P<0.001	-47 (-56 to -35); -P<0.001
Relative to oseltamivir group	-	-	- 5.0 (-22 to 17); P=0.65	- 19 (34 to -0.3); P=0.047
Relative to MY group	-	-	-	-15 (-30 to 4); P=0.122
Results				
• Oseltamivir and MY had similar effects on alleviating fever • Compared with oseltamivir, the combination therapy group was better in fever resolution (p=0.05)				

Table 2: Comparison of times taken to alleviate fever in the control group and three treatment groups. (CI = confidence interval).

	Oseltamivir group		MY group	
Daily treatment costs	55.2 RMB	8.06 USD	16 RMB	2.33 USD
Cost over duration of treatment	276 RMB	40.31 USD	80 RMB	11.68 USD

Table 3: Comparison of average costs per patient of treatment of the oseltamivir and MY patient groups.

Safety

Two patients in the MY group had nausea and vomiting. No side effects were observed in the control, oseltamivir, or combination therapy group. No differences were observed in complications after treatment among the four groups.

Cost

Although treatment by both oseltamivir and MY was effective, treatment costs in the MY group averaged 16 RMB (2.33 USD) per day (80 RMB or 11.68 USD over the duration of treatment), compared to 55.2 RMB (8.06 USD) per day in the oseltamivir group (or 276 RMB or 40.31 USD over the course of treatment). This equates to savings of over 70% (Table 3).

Partnerships

This was a multicentre research project and was completed through the collaboration of 11 medical centres, including Beijing Chao-Yang Hospital, Beijing Institute of Respiratory Medicine; Beijing Hospital, Ministry of Health; Dongzhimen Hospital affiliated to Beijing University of Chinese Medicine; Yantai Infectious Disease Hospital, Shan-dong; Chengdu Infectious Disease Hospital, Sichuan; Beijing Haidian Hospital, Beijing; Beijing Ditan Hospital, Institute of Infectious Diseases, Capital Medical University, Beijing; Renmin Hospital of Wuhan University; Changxindian Hospital of Fengtai District of Beijing; Second Hospital of Chaoyang District of Beijing, Beijing; West China Medical School, West China Hospital, Sichuan University, Sichuan.

In addition, serial real-time RT-PCR for viral RNA titres was carried out with assistance of local branches of the Chinese Centre for Disease Control and Prevention.

Impact

The research results were acknowledged by renowned international institutions, and were published in the Annals of Internal Medicine as original research. The project made up an indispensable part of a set of research achievements that won the First Class Prize of the State Scientific and Technological Progress Award, and the First Prize of the Beijing Science and Technology Awards.

The research results were reported many websites, such as the New York Times and Reuters. The journal article was included in five international authoritative medical databases, including PIER (Physician's Information and Education Resource), Science-Based Medicine, NHS, EBSCO and Tripdatabase.

The project also won an international honour for the medical response work done by China, and also helped to promote TCM on the international market.

Replicability

We have shown that MY could be an effective, more economic solution to the widespread use of oseltamivir.

Policy Implications

The project innovated the "Fever Theory" of TCM, and the research results provide strong evidence for guidelines for the use of TCM in the treatment of influenza, as well as a basis for the further exploration of TCM that has been used for the treatment of seasonal influenza for thousands of years. Therefore, the treatment was well accepted by the public.

Future Plans

Based on the work done, we will further explore other TCMs for treating pneumonia. We also aim to explore the mechanism of action of MY using animal models and in vitro experiments. In addition, we will collaborate with other medical centres to perform multicentre clinical trials, as well as strengthening the collaboration with basic research teams to understand the mechanisms, by which TCMs achieve their protective effect in patients.

Publications

- Wang C., Cao B., Liu Q.Q., et al. (2011). Oseltamivir compared with the Chinese traditional therapy maxingshigan-yinqiaosan in the treatment of H1N1 influenza: a randomized trial. *Ann Intern Med*, 155(4):217-225.
- Yang SG, Cao B, Liang LR, et al. (2012). Antiviral therapy and outcomes of patients with pneumonia caused by influenza A pandemic (H1N1) virus. *PloS One*, 7(1):e29652.

Additional contributors

Bin Cao, MD, Qing-Quan Liu, Zhi-Qiang Zou, Zong-An Liang, Li Gu, Jian-Ping Dong, Li-Rong Liang, Xing-Wang Li, Ke Hu, Xue-Song He, Yan-Hua Sun, Yu An, Ting Yang, Zhi-Xin Cao, Yan-Mei Guo, Xian-Min Wen, Yu-Guang Wang, Ya-Ling Liu, Liang-Duo Jiang, Jing Zhao, Lai-Ying Fang, Zhi-Tao Tu, Chun Huang, Xiao-Hui Zhai, Xiao-Li Li, Wei Wu, Ran Li, Yi-Qun Guo, Jing-Ya He, Yong Guo, Yu-Dong Yin, Shufan Song, Na Cui, Lu Bai, Ling-Ling Su, Getu Zhaori, Weili Zhang, Yiqing Song, Hua-Xia Chen, Chun-Jiang Zhao, Xiao-Min Yu, Ran Miao, Ying-Mei Liu, Li-Li Ren and Xiang-Yang Ding.

References

- Wang *et al*. Chinese Archives of Traditional Chinese Medicine (2007). 25: 2200-3.
- Wang J., Cheng S-h., Zhang J-j. (2007). A Systematic Review of Chuanhuning for acute respiratory treat infections, 25:2200-2203.