Gingyo Gedokusan vs Oseltamivir for the Treatment of Uncomplicated Influenza and Influenza-like illness: An Open-label Prospective Study

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Background: Gingyo-gedoku-san (GGGS) is an herbal medicine approved for upper respiratory infections in Japan. We conducted an open-label, multi-center, prospective trial, comparing GGGS with oseltamivir in patients with influenza and influenza-like illness (ILI) as a pilot study.

Methods: Subjects were healthy persons aged between 16 and 40, and were enrolled from January 12, 2010 to March 24, 2011. Fifteen patients were enrolled in this trial (8 and 7 for GGGS and oseltamivir, respectively). RT-PCR was positive for pandemic influenza A (H1N1) in 10 patients. The patients were provided with either GGGS or oseltamivir for 5 days. The primary outcome was mortality and/or hospitalization 7 days after the initial diagnosis. Body temperature and other clinical characteristics were also evaluated.

Results: All patients recovered from illness without complication or hospitalization. The mean time to resolve symptoms for the GGGS and oseltamivir groups was 3.9 days and 3.3 days, respectively (p = 0.43). The GGGS group appeared to have a smaller symptom score AUC than the oseltamivir group, (p = 0.26). Time to recover activity level appeared to be shorter in the GGGS group (p = 0.10), with shorter time to recover health status (p = 0.02). Sub-group analysis on patients with positive PCR showed similar results between the two groups.

Conclusion: GGGS was associated with symptom improvements resembling oseltamivir for both influenza and ILI. Randomized controlled trials involving larger sample sizes are needed to confirm these results.

INTRODUCTION

The use of neuraminidase inhibitors is usually recommended for hospitalized patients, or those presenting with clinical co-morbidities. However, it remains uncertain whether these medications should be universally administered to patients presenting with no risk factors. Both the Centers for Disease Control and Prevention (CDC) in the United States and the National Institute of Health and Clinical Excellence (NICE) in the United Kingdom do not advocate the use of anti-influenza medications for those without risk factors. On the other hand, the Japanese Association for Infectious Diseases (JAID) recommends the use of neuraminidase inhibitors even for patients that have no underlying risk factors or those that do not require hospitalization. These recommendations, however, are largely based on expert opinion and not on concrete clinical evidence.

It is well-recognized that the use of neuraminidase inhibitor can effectively shorten the symptomatic period of influenza. In addition, evidence suggests that the early use of certain neuraminidase inhibitors may decrease mortality and hospitalization due to influenza—in particular pandemic 2009 influenza A H1N1. However, the application of neuraminidase inhibitors to every case of influenza may pose serious threats to patient safety and public health, including adverse effects, the emergence of drug resistance, and rising medication expenses. Overuse of neuraminidase inhibitors can also lead to logistical problems, particularly during a pandemic.

GGGS is an herbal medication containing extracts from plants and animal products. GGGS is approved for over the counter (OTC) use to treat upper respiratory infections in Japan. However, its efficacy against influenza has not been evaluated at the clinical investigative level. Therefore, we conducted a pilot study aimed at evaluating the efficacy of GGGS against influenza and influenza-like illness (ILI) in comparison to a globally recognized neuraminidase inhibitor, oseltamivir.

MATERIALS AND METHODS

Study design

This is an open-label, unblinded, multi-center, prospective comparative study, comparing GGGS with oseltamivir in the management of influenza and ILI. Influenza has gained notoriety in Japan, largely due to the 2009 pandemic that struck the country. Both the Japanese government and its citizens have
become increasingly anxious about this disease, and this has led clinicians to use neuraminidase inhibitors routinely in Japan. This tendency made it very difficult for us to conduct a randomized double-blinded study, thus we designed a less desirable yet more acceptable open-label trial without randomization.

Settings
The study was conducted at a walk-in outpatient clinic at Kobe University Hospital, Kobe, Japan, and 4 private outpatient clinics in the Kansai area, Honshu (Main island), Japan.

Patients
Subjects were healthy persons aged between 16 to 40 years old. Patients presenting with a fever above 38°C, respiratory symptoms, such as cough and sore throat, and onset of symptoms within the past 48 hours were diagnosed as influenza-like illness (ILI), and were eligible for enrollment in the study. Patients with underlying medical conditions, those who were pregnant, and those requiring hospitalization were excluded from the study. Written informed consent was obtained from each participant. The study was conducted from January 12, 2010 to March 24, 2011. The study was originally intended to enroll approximately 100 patients; however, it was decided to terminate the study in March 2011 due to an unexpectedly low number of subjects enrolled and a lack of funding.

This study was approved by the Institutional Review Board at Kobe University School of Medicine (IRB approval number: #988) and was registered in the University Hospital Medical Information Network Clinical Trials Registry (trial number UMIN000002676).

Gingyo-gedoku-san (GGGS)
GGGS preparation is a mixture of 9 plants and 1 animal ingredients. The following were mixed with trehalose, magnesium aluminometasilicate, hydroxypropyl methylcellulose, anhydrous silicic acid, and cornstarch to make 7.5 g extract (daily dose for adults): *Lonicerajaponica* Thunb. 4.26 g; *Forsythia suspensa* Thunb. 4.26 g; *Mentha arvensis* L. var. *piperascens* MALINV. 2.556 g; *Schizonepeta tenuifolia* Briq. 1.704 g; *Glycine max* Merr. (fermented soybean) 2.136 g; *Glycyrrhiza glabra* 2.556 g; *Platyodon grandiflorum* A. DC. 2.556 g; *Lophatherum gracile* Brongn 1.704 g; seeds of *Arctium lappa* L. 2.136 g; and powdered horn of *Saiga tatarica* 0.132 g. GGGS was provided by Rhotopharmaceutical Co., Ltd.

Intervention
An open-label unblinded study was conducted with Gingyo-gedoku-san (GGGS) 2.5 g three times a day orally for 5 days. Oseltamivir 75 mg was provided twice daily orally for 5 days. Patients were provided with information regarding both medications and were offered the option to choose either one freely. Also, patients were instructed not to take any other medications during the study period, including antipyretics, such as acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs).

Axillary temperature was recorded twice a day (morning and evening) and the severity of seven predetermined symptoms (nasal stuffiness, sore throat, cough, muscle aches, tiredness or fatigue, headache, and feverishness) were individually rated by the patients, daily up to day-7 using a four-point scale (0, none; 1, mild; 2, moderate; 3, severe), as in previous studies. Additionally, an 11-scale subjective activity level (from 0, not able to do anything to 10, usual activity level) and subjective health status (from 0, the worst health status the patient can imagine, to 10, the best health status of the patient) was recorded daily up until day-7. The patients were instructed to notify their physician immediately if they noticed any worsening in their symptoms, any potential adverse effects of the medications, or if they had any other pertinent concerns. Influenza-related clinical events were defined as the incidence of a secondary complication (such as pneumonia) or worsening of symptoms requiring a revisit to the clinic or hospitalization. Patients reported treatment compliance using a self-administered questionnaire.

Detection of viral RNA
Diagnosis of influenza was made by Reverse Transcription Polymerase Chain Reaction (RT-PCR)
of samples obtained from nasal swab or throat washings procured at the time of visit. Samples were sent to the Division of Zoonosis at Kobe University Graduate School of Medicine (Y. M. and K. S.), where RT-PCR was carried out.

RNA was extracted and isolated from samples by using the QIAamp Viral RNA Mini Kit (Qiagen K. K.-Japan, Tokyo, Japan). The RNA was then subjected to one step RT-PCR using Super Scripts III One-step RT-PCR System with Platinum® Taq DNA Polymerase (Invitrogen, U.S.A.).

Results

Since there was a genuine concern for increased mortality without the use of neuraminidase inhibitors in Japan during the study period, relatively conservative primary outcomes were selected. Consequently, the primary outcomes selected became mortality and/or hospitalization at day-7 after the initial diagnosis.

Secondary outcomes were total symptom score AUC (area under the curve), total subjective activity level AUC, total subjective health status AUC, time to alleviation of illness, time to recovery of subjective activity level and health status. The time to alleviation of illness was defined as the time from the beginning of the study treatment to the time that 7 key symptoms typical of natural influenza had reduced to absent or mild.6,7 Time to recovery of subjective activity level and health status was defined as score achievements of 8 or above.

Statistics

All statistical tests were 2-sided, and we considered a p value<0.05 to be statistically significant. Student’s t-test was used for comparisons of two group characteristics. Wilcoxon rank-sum test was used to compare differences in AUC values. The time to alleviation of symptoms, the time to recovery of activity level and health status was compared using a logrank test. Analyses were performed using STATA version 11 for Macintosh (StataCorp, College Station, TX).

RESULTS

In total 15 patients were enrolled in this trial. Median age was 28 (range 17–39). Patient characteristics are provided in Table 1. As per inclusion criteria, no patient had any underlying medical condition. One patient had a history of an elbow fracture and another had received LASIK (Laser-assisted in situ keratomileusis) eye surgery for myopia. We did not consider these as underlying medical conditions. Only one patient was vaccinated for influenza in the previous autumn. This patient developed influenza A during the study period and was administered GGGS. One patient in the GGGS group disclosed that he took one tablet of over the counter NSAIDs during the study period. Meanwhile, another patient in the oseltamivir arm disclosed that he received 500 ml of intravenous normal saline hydration on day 3, when he returned to his primary physician with headache. We judged these patients who received these treatments eligible for inclusion in the analysis. Every patient completed the trial.

RT-PCR was positive for pandemic influenza A (H1N1) in 10 patients. No other influenza virus was detected (Table 1).

By day–7, every patient had recovered from illness. One patient discontinued GGGS due to somnolence during daytime and the bitter taste of the medication. Only one patient in the oseltamivir group reported adverse event (headache as aforementioned).

The mean times to resolve symptoms for the GGGS group and oseltamivir were 3.9 days (95% CI 2.83–4.92) and 3.3 days (95% CI 2.06–4.60) respectively (p=0.43). The times to resolve symptoms restricted to patients with positive PCR results were 3.2 days (95% CI 1.84–4.92) and 3.6 days (95% CI 1.72–5.48) respectively (p = 0.43). The GGGS group appeared to have smaller symptom score AUCs than the oseltamivir group; however, the documented difference was not statistically significant (Figure 1A, p=0.26), even among those with positive PCR results (Figure 1B, p=0.29). Body temperature measured by the patients exhibited no difference between the two groups, even when the patients with positive PCR were analyzed (Figure 2A, 2B).

For activity level, the mean time to recover activity
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>GGGS</th>
<th>Oseltamivir</th>
</tr>
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<tbody>
<tr>
<td>n male (%)</td>
<td>7(87.5)</td>
<td>7(100%)</td>
</tr>
<tr>
<td>Mean age (± SD)</td>
<td>27.3±3.5</td>
<td>28.6±7.5</td>
</tr>
<tr>
<td>Completion of the medication</td>
<td>8(100%)</td>
<td>7(100%)</td>
</tr>
<tr>
<td>Virus type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/Russian H1N1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>A/pandemic H1N1 2009</td>
<td>6(75%)</td>
<td>4(57.1%)</td>
</tr>
<tr>
<td>A/Hong Kong H3N2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No influenza virus detected</td>
<td>2(25%)</td>
<td>3(42.9%)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>0(0%)</td>
<td>1(14.3%)</td>
</tr>
<tr>
<td>ex-smoker</td>
<td>1(12.5%)</td>
<td>1(14.3%)</td>
</tr>
<tr>
<td>non-smoker</td>
<td>7(87.5%)</td>
<td>5(71.4%)</td>
</tr>
<tr>
<td>Baseline symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline vital signs: mean (SD)</td>
<td>8.6(5.3)</td>
<td>8.7(3.5)</td>
</tr>
<tr>
<td>Body temperature</td>
<td>37.9(0.7)</td>
<td>38.1(1.1)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>121.6(19.5)</td>
<td>117.6(16.0)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>78.3(13.0)</td>
<td>77.4(12.8)</td>
</tr>
<tr>
<td>Respiratory rate (/minute)</td>
<td>19.1(5.9)</td>
<td>20.6(10.0)</td>
</tr>
<tr>
<td>Baseline oxygen saturation, SpO2 (%)</td>
<td>98.1(0.7)</td>
<td>97.3(0.8)</td>
</tr>
<tr>
<td>Subjective activity level (0–10) mean (SD)</td>
<td>3.9(2.0)</td>
<td>4.6(2.8)</td>
</tr>
<tr>
<td>Subjective health status (0–10) mean (SD)</td>
<td>4.9(2.0)</td>
<td>6.0(2.5)</td>
</tr>
</tbody>
</table>

level appeared shorter in the GGGS in comparison to the oseltamivir group (3.3 days [95% CI 2.18–4.32] vs 4.3 days [95% CI 2.75–5.91], p = 0.10), even when only PCR positive cases were analyzed (3.4 days [95% CI 1.98–4.82] vs 5.0 days [95% CI 3.48–6.52], p = 0.07). A smaller activity level AUC in the GGGS was also observed (Figure 3A, p = 0.09). This difference, however, was not as apparent when only patients with positive PCR results were analyzed (Figure 3B, p = 0.29).

For subjective health status, the time to recover health status was shorter for the GGGS group and the difference was statistically significant (Figure 4A, 3.0 days [95% CI 1.80–4.19] vs 5.0 days [95% CI 3.67–6.32], p = 0.02), and those with positive PCR (Figure 4B, 3.4 days [95% CI 1.73–5.07] vs 5.3 days [95% CI 3.73–6.77], p = 0.054).

DISCUSSION

Influenza and influenza-like illness (ILI) are associated with significant morbidity and mortality. Although influenza can be prevented by vaccination, efficacy and effectiveness are limited. Adamantanes, such as amantadine and rimantadine, used to be drugs of choice for influenza but they are no longer recommended due to potentially serious central nervous system side effects, inefficacy against influenza B, and increasing resistance in influenza A. These drugs may, however, be effectively combined with other medications to augment their efficacy.

Neuraminidase inhibitors, such as oseltamivir and zanamivir, are both effective against influenza A and B. These drugs may, however, be effectively combined with other medications to augment their efficacy.

Newer neuraminidase inhibitors, such as permeir and laninamivir, have been recently introduced and are equally effective against influenza virus infections.

However, overuse of neuraminidase inhibitors may pose a number of problems. For example, oseltamivir resistance became common in seasonal influenza A (H1N1). Oseltamivir resistance is also found in other types of influenza. Peramivir is considered to have the same mechanism of developing resistance with oseltamivir (H275Y mutation). Zanamivir resistance is rare but documented to occur. Zanamivir is not recommended for those with asthma or other
Figure 1. Symptom score AUCs for the GGGS group and the oseltamivir group on ILI (A) and PCR confirmed influenza (B). GGGS, Gingyo Gedoku San. ILI, influenza-like-illness.

Figure 2. Body temperature for the GGGS group and the oseltamivir group on ILI (A) and PCR confirmed influenza (B). GGGS, Gingyo Gedoku San. ILI, influenza-like-illness.

Figure 3. Activity level for the GGGS group and the oseltamivir group on ILI (A) and PCR confirmed influenza (B). GGGS, Gingyo Gedoku San. ILI, influenza-like-illness.

Figure 4. Patients’ subjective health status for the GGGS group and the oseltamivir group on ILI (A) and PCR confirmed influenza (B). GGGS, Gingyo Gedoku San. ILI, influenza-like-illness.
underlying respiratory illness due to a potentially life threatening side effect (bronchospasm). Gastrointestinal side effects are also relatively common among those who received oseltamivir. Neuropsychiatric side effects are also a serious concern with oseltamivir, although the association between this side effect and oseltamivir remains controversial. And lastly, stockpiles of antiviral agents may be exhausted, particularly during long-lasting pandemics.

Diagnosis of influenza is another problem with the use of neuraminidase inhibitors. Rapid influenza diagnostic tests (RIDTs) are widely used but have relatively low sensitivity (40–70%), especially shortly after the onset of illness. More accurate diagnostic tests, such as immunofluorescence, RT–PCR, and viral cultures, are laborious, time consuming, and are not practical in the management of patients with influenza. The CDC recommends use of neuraminidase inhibitors, even if RIDTs are negative, if influenza is clinically suspected and further recommends that physicians not wait until diagnosis is confirmed. This means that many patients will receive a neuraminidase inhibitor for ILI, regardless of whether the influenza virus is present or not. Therefore, medications effective against ILI caused by pathogens other than influenza virus are expected to be relevant and meaningful in a clinical context.

Gingyo-gedoku-san (GGGS) is an herbal medicine containing extracts from plants and animal products and is available OTC in Japan. Although it is approved for use in upper respiratory infections, its efficacy against influenza and ILI has never been investigated.

GGGS is similar to Gingyo-san (GGS, Yinqiaosan in Chinese pronunciation) but one of its ingredients, Reed rhizome (root of Phragmites communis Trin.), is replaced by Antelopis Cornu (horn of Saiga tatarica, antelope). In traditional Chinese medicine, Gingyo-san (GGS) has been commonly used to treat the common cold and bronchitis. Antelopis Cornu is claimed to have antipyretic and sedative effects.

Few studies exist on GGGS but there exist a number of studies on GGS. GGS has an antipyretic quality and exerts antiviral effects. In addition, GGS has the efficacy of clearing away heat, relieving pain, counteracting hypersusceptibility, and counteracting bacterial and viral infections. GGS has shown therapeutic effects on bacterial and viral infections in mice. The antipyretic action of GGS regulates elevated serum IL-1 levels produced in influenza–infected mice. In addition, two components contained in GGS were shown to have antiviral qualities in mice infected with influenza virus. In a murine model, GGS showed immunomodulatory effects against lipopolysaccharide induced lung inflammation. Although clinical efficacy of traditional Chinese Medicines has been doubted due to lack of well-designed clinical trials, a recent randomized controlled trial compared the combination of GGS and Makyo-Kanseki-To (Maxingshigan in Chinese pronunciation) against oseltamivir for the treatment of H1N1 influenza, and the results were comparable, suggesting that traditional Chinese medicines may be effective alternatives to neuraminidase inhibitors.

The present study is a pilot study to investigate the efficacy of GGGS against influenza and ILI. For both confirmed influenza and ILI, the results of GGGS were comparable to oseltamivir, and there were no cases of hospitalization or mortality (our primary outcomes). Time to recovery appeared shorter in patients administered GGGS in comparison to patients provided with oseltamivir. There were no significant adverse effects observed in the present study. Oseltamivir is not expected to be effective against ILI, but in actual practice, it is often used due to the lack of rapid and accurate tests for influenza. Therefore, including patients with ILI in this study was considered relevant and logical from a clinical perspective.

There is some expert opinion that the mortality due to the pandemic influenza in 2009 was very low in Japan because most patients received neuraminidase inhibitors. However, the recent Cochrane reviews did not demonstrate evidence of neuraminidase inhibitors preventing complications or hospitalization. In order to maintain stockpiles of medications on reserve for genuine pandemics, to prevent the emergence of drug resistance, and to avoid unnecessary side effects, the universal application of neuraminidase inhibitors to uncomplicated
influenza should be granted reconsideration and further studies are imperative in justifying this ongoing practice.

On the other end of the spectrum, the efficacy of alternatives, such as traditional Chinese medicines, should be closely studied. Increasing the number of treatment options will only serve to benefit patients with influenza and ILI.

A major limitation of this study is its limited size. Secondly, we were not able to conduct a randomized controlled trial and instead conducted an open-label study, mainly because of the panicky atmosphere in Japan during influenza season due to fears of pandemic. Since we did not randomize the patients, selection bias may have affected the study results. For example, although there was no statistical difference between two groups (data not shown), there appeared more male in GGGS group (87.5% vs 57.1%). Since citizens are calmer as of this writing, larger clinical trials with randomization may be possible. Finally, we did not examine the oseltamivir resistance in confirmed influenza, but the incidence in Japan during that period was quite low (0.5%), which makes the risk almost negligible.

CONCLUSION

Although we were not able to evaluate our primary outcome such as mortality due to the small sample size, our results suggest that GGGS may be as effective as oseltamivir in the management of uncomplicated influenza and ILI in adults. GGGS may be a potential alternative to mainstream pharmaceuticals that could be beneficial if adopted in clinical practice. Further studies are needed to confirm our findings.

Conflicts of Interest

Rhoto Pharmaceutical Co., Ltd., provided funding and GGGS for use in this study.

The main results of this study were presented at the Conference on ‘Influenza Antivirals: Efficacy & Resistance’, 8–10 November 2011, Rio de Janeiro, Brazil

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References


9 Kohno, S; Kida, H.; Mizuguchi, M. et al.


