Preliminary study of a traditional Chinese medicine formula in systemic lupus erythematosus patients to taper steroid dose and prevent disease flare-up

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- Steroid
- Systemic lupus erythematosus
- Traditional Chinese medicine

Abstract  Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease. Prolonged complete remission is rare. Most patients with SLE need long-term treatment with glucocorticoid and immunomodulators. However, side effects because of the above medications are common. We evaluated the effect of adding-on Dan-Chi-Liu-Wei combination (DCLWC) on SLE patients with conventional therapy in tapering steroid and preventing disease flare-up. This was a double-blind and randomized controlled trial. Sixty-six SLE patients were recruited into this study and 53 patients who fulfilled the 1997 revised criteria for the classification of SLE with an SLE disease activity index (SLEDAI) score of 2–12 and a steroid (measured with prednisolone) daily dose of less than 20 mg/d were enrolled. The patients were randomized into either an experimental or control group. We checked the urine analysis, hemogram, liver function, renal function, C3, C4, erythrocyte sedimentation rate, and...
anti-dsDNA, evaluated the SLEDAI score, and recorded the steroid dose at 0 months, 3 months, and 6 months, respectively. After 6 months of study, the C4 and blood urea nitrogen level revealed a statistically significant difference in either group. There was a tendency toward a decreased SLEDAI score in the experimental group ($p = 0.083$) but not in the control group ($p = 0.867$). The steroid dose was not statistically significant in either group. Renal function and liver function revealed no statistically significant statistics changes in either group. Adding-on DCLWC to conventional therapy for the treatment of SLE was safe and might have a borderline effect in decreasing disease activity, but it was not possible to taper the dosage of steroid after 6 months of clinical trial. Therefore, a long-term follow-up and a large-scale study are necessary to confirm the effect of DCLWC.

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### Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease predominantly involving childbearing women. Although the 10-year survival rate for SLE patients has improved up to 80%–90%, complete cure is rare. Most patients with SLE need long-term treatment with glucocorticoids and immunomodulators to control disease activity. However, prolonged complete remission in lupus is rare [1]. Long-term steroid use can lead to a variety of side effects, including central obesity, moon face, buffalo hump, wasting of the extremities, osteoporosis, avascular necrosis of bone, and infection. Therefore, the best way to taper the steroid dose while concomitantly preventing disease flare-up is an important issue to date.

At present, antimalarial drugs and immunosuppressive agents, such as azathioprine or cyclophosphamide, have been used to resolve the above-mentioned problems. However, side effects because of these medications are common. Antimalarial drugs can cause macular damage [2] and myopathy [3]. Azathioprine can cause myelosuppression [4], hepatotoxicity [5], and lymphoproliferative disorders [6]. Cyclophosphamide can cause immunosuppression [7], infertility [8], and bladder cancer [9]. Because of their concern about these side effects, most SLE patients look desire to an alternative therapy [10,11].

Traditional Chinese medicine (TCM) is one of the most well-organized complementary and alternative medicine systems, with more than 2,000 years of clinical experience. Therefore, we wanted to find an alternative treatment using TCM to help SLE patients achieve long-term health, with a lower steroid dose and less disease flare-up. Our research team included immunologists, TCM experts, and a pharmacy specialist who designed the Dan-Chi-Liu-Wei combination (DCLWC), which is composed of two classical formulas: Liu-Wei-Di-Huang Wan (LWDHW) and Dan-Chi San (also known as Fufang Danshen tablets). LWDHW, one of the most famous TCM formulas, was originated by Qian-Yi, a TCM physician in the Northern Sung Dynasty (960–1127 A.C.). Recent studies have revealed that LWDHW has immunosuppressive effects [12].

Dan-Chi San, also known as Fufang Danshen tablets, originated at the Shanghai Secondary Pharmaceutical Factory of Traditional Chinese Medicine. It was developed in 1975 and has been produced since 1977. It is a common TCM and has been used for the treatment of coronary artery disease in China for more than 30 years [13], and it has been documented in the Pharmacopoeia of the People’s Republic of China from the third edition (1977) [14]. There are other preparations, such as Compound Danshen Drip-Ping Pill [15] and a compound injection of Danshen. It has been reported that Dan-Chi San has biological activities that improve microcirculation, dilate coronary artery, and improve myocardial ischemia. In clinical practice, it has been used clinically for coronary artery disease, cardiac angina, diabetes microvascular complications, and atherosclerosis [16–18]. Women with SLE have strikingly higher rates of premature cardiovascular disease, with up to a 50-fold increase in the incidence of cardiovascular complications over age- and sex-matched control subjects [19].

Taken together, the DCLWC is accepted to be beneficial in tapering the steroid dose and decreasing the frequency of disease flare-up in SLE patients. Therefore, we evaluated the effect of DCLWC on SLE patients, using a double-blind and randomized controlled trial.

### Material and methods

#### Recruitment of patients

This trial was performed at Chang Gung Memorial Hospital-Kaohsiung Medical Center and Chung-Ho Memorial Hospital, Kaohsiung Medical University from February 2007 to December 2007 (Clinical trial registration number: ISRCTN73842582). The study protocol was evaluated and approved by the Institutional Review Boards of Chang Gung Memorial Hospital-Kaohsiung Medical Center and Chung-Ho Memorial Hospital. We recruited SLE patients from the outpatient clinic. All participants gave their written informed consent, which was approved by the Institutional Review Board. Inclusion criteria were all of the following: patients meeting the 1997 revised criteria for the classification of SLE [20], SLE disease activity index (SLEDAI) score [21] of 2–12, and a steroid (measured with prednisolone) daily dose less than 20 mg/d, the minimum dose being 2.5 mg/d.

Exclusion criteria were as follows: pregnancy, age under 18 or more than 60 years, and renal function impairment (serum creatinine level higher than 1.4 mg/dL).

#### Study design

This was a double-blind, randomized controlled trial. SLE patients with mild-to-moderate disease activity (SLEDAI 2–12) were recruited and randomly assigned to either
a control or an experimental group. Simple randomization was achieved using a sequence of random numbers from a computer-generated sequence. "T" was allocated to "experiment" and "C" to "control". In the "T" group, patients were treated with conventional medicines and 100% TCM. In the "C" group, patients were treated with conventional medicines and 10% TCM. All TCM packages, including both experimental and control groups, were marked with sequence number only. Neither patients nor doctors or research assistants knew the content of TCM packages. The sequence of random numbers was sealed in a box with signature by the principle investigator until the study was completed. All SLE patients were allowed to continue their original therapy using Western medicine, including glucocorticoid, antimalaria drugs, and/or other immunomodulators.

DCLWC is composed of two well-known formulas: LWDDH (Table 1) and Dan-Chi San (Table 1). The study medication was administered as pills within a package to both experimental and control groups. The experimental group received a package of TCM each time via oral intake in total three times per day as an add-on therapy. Each package contained 2.7 g of LWDDH and 125 mg of Dan-Chi San (100%) together. The dosage was given according to the manufacturer’s instructions. In the control group, 10% of LWDDH with 90% starch and 10% Dan-Chi San with 90% starch were used.

The primary outcome was the change of steroid dosage after 6 months of combined therapy (DCLWC and regular medications). The secondary outcome was the frequency of disease flare-up and the change in the immunologic index (C3, C4, anti-dsDNA) after 6 months of combined therapy.

Evaluation of adverse effects

Adverse effects, including abdominal pain, dyspepsia, constipation, diarrhea, edema, headache, abnormal renal function test, abnormal liver function test, and abnormal hematologic test were recorded. All patients were quested systemically at the 3rd and 6th months of this study, respectively.

Laboratory test and evaluation of disease activity

Complete blood routine, erythrocyte sedimentation rate, urine analysis, blood urea nitrogen (BUN), creatinine, alanine transaminase, aspartate transaminase (AST), C3, C4, anti-dsDNA were measured at baseline, 3 months, and 6 months, respectively. The disease activity of SLE was evaluated at baseline, 3 months, and 6 months, using the SLEDAI developed by Bombardier et al. [21]. If SLEDAI score increased more than 3 compared with previous SLEDAI score, it was regarded as disease flare-up [22].

Statistics

Statistical analyses were performed with Statistics Package for Social Science software 11.5 for windows (SPSS Inc., Chicago, IL, USA). Descriptive data were presented as mean ± standard deviation as required according to the normal distribution of the parameters. Figures were pictured with repeated measurements. Statistical comparison between DCLWC experimental or control group was performed using the analysis of variance, whereas the paired t test was used for comparison between pre- and posttreatment. Statistically significant probability was expressed as p value less than 0.05.

Results

Patient enrollment and assignment

We opened this trial, including inclusion criteria by poster, to 502 patients with SLE; followed up at outpatient department of Chang Gung Memorial Hospital-Kaohsiung Medical Center and Chung-Ho Memorial Hospital, Kaohsiung Medical University. Sixty-six volunteers volunteered for the trial. After screening, 53 patients who fulfilled the enrollment

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**Table 1** Composition of Dan-Chi-Liu-Wei combination

<table>
<thead>
<tr>
<th>Liu-Wei-Di-Huang Wan</th>
<th>Dan-Chi San</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scientific name of Chinese herbs</strong></td>
<td><strong>Amount of every 25 g extractum (g)</strong></td>
</tr>
<tr>
<td>Radix Rehmanniae Preparata*</td>
<td>8</td>
</tr>
<tr>
<td>Rhizoma Dioscoreae*</td>
<td>4</td>
</tr>
<tr>
<td>Poriae*</td>
<td>3</td>
</tr>
<tr>
<td>Cortex Moutan Radicis*</td>
<td>3</td>
</tr>
<tr>
<td>Rhizoma Alismatis*</td>
<td>3</td>
</tr>
<tr>
<td>Fructus Corni*</td>
<td>4</td>
</tr>
</tbody>
</table>

Every 8 g of extract fine granules contained 4 g starch and 4 g extractum from Chinese herbs. The ratio of the six Chinese herbs (marked "**") and the extractum (marked "*")) is 25:4 = 6.25:1. Starch was used as an excipient in Liu-Wei-Di-Huang Wan combination.

* Polyethylene glycols were used as an excipient in Dan-Chi San.
criteria were randomly assigned to either the control or the experimental group (Fig. 1). Forty-eight patients completed 3 months of the trial, and 46 completed 6 months. The baseline characteristics of both groups that completed 6 months study showed no significant differences (Table 2). No patients changed any disease-modifying antirheumatic drugs, such as hydroxychloroquine and azathioprine; only steroid dose was adjusted according to disease activity during the study period.

Steroid dosage change

There was no significant change of steroid dose after 6 months in the experimental (\(p = 0.715\)) (Table 3) or control group compared with baseline (\(p = 0.947\)) (Table 3).

Frequency of disease flare-up

During the 6-month period of DCLWC add-on therapy, the frequency of disease flare-up in the experimental group was 8.6% (2/23, 2 patients with 2 flare-ups). This was lower than the 13% (3/23, 3 patients with 4 flare-ups) in the control group. There was no significant difference between the two groups. However, there was one very severe disease flare-up resulting in admission in the control group, in a patient who suffered two flare-ups in the course of study, but there were no severe disease flare-ups in the experimental group.

SLEDAI score

In the experimental group, there was a tendency toward a decreased SLEDAI scores after 6 months of DCLWC add-on therapy compared with baseline (\(p = 0.083\)) (Table 3). In contrast, there was no significant change in the control group compared with the base line (\(p = 0.867\)) (Table 3).

Serologic change

Anti-dsDNA

There was no significant change of serum level of anti-dsDNA after 6 months in the experimental (\(p = 0.157\)) (Table 3) or control group compared with base line (\(p = 0.942\)) (Table 3).

C3 and C4 level

There was no significant change in the serum level of C3 after 6 months of DCLWC add-on therapy in the experimental group (\(p = 0.978\)) (Table 3) or in the control group (\(p = 0.123\)) (Table 3). There was a significant elevation of the serum level of C4 after 6 months of DCLWC add-on therapy in the experimental group (\(p < 0.01\)) (Table 3) and in the control group (\(p < 0.01\)) (Table 3).

Erythrocyte sedimentation rate

There was a no significant change in the serum level of erythrocyte sedimentation rate after 6 months of DCLWC add-on therapy in the experimental group (\(p = 0.241\)) (Table 3) or in the control group (\(p = 0.116\)) (Table 3).

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**Table 2** Demographic and baseline characteristics of patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control (n = 23) (mean ± SD)</th>
<th>Experimental (n = 23) (mean ± SD)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>36.26 ± 9.70</td>
<td>36.21 ± 8.90</td>
<td>0.987</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>108.52 ± 11.52</td>
<td>111.21 ± 14.16</td>
<td>0.483</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>68.60 ± 9.25</td>
<td>72.08 ± 9.65</td>
<td>0.219</td>
</tr>
<tr>
<td>Heart rate (bpm/min)</td>
<td>77.56 ± 7.93</td>
<td>79.39 ± 9.21</td>
<td>0.475</td>
</tr>
<tr>
<td>Body height (cm)</td>
<td>158.52 ± 5.08</td>
<td>160.43 ± 5.79</td>
<td>0.241</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>51.78 ± 9.22</td>
<td>56.39 ± 7.86</td>
<td>0.075</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.55 ± 3.16</td>
<td>21.96 ± 3.28</td>
<td>0.146</td>
</tr>
</tbody>
</table>

Basic data of the experimental and control group patients who completed the 6-month trial. BMI = body mass index; bpm = beats per minute; SD = standard deviation.
This was the first double-blind randomized controlled trial using TCM add-on therapy to taper steroid dose while concurrently preventing disease flare-up. Only 4 patients experienced adverse effects, which included gingivitis, skin rash, diarrhea, and a sore throat. There was no significant change in the disease activity index (SLEDAI) after 6 months of TCM add-on therapy, but the SLEDAI score showed a decreasing tendency in the experimental group. Real compliance of patients was 11.08% and in the experimental group was 0.8%. There was no difference in the frequency of adverse effects between the two groups.

**Adverse effects**

- Antid-dsDNA (IU/mL) 62.83 ± 7.21
- BUN (mg/dL) 16.32 ± 9.67
- C3 (mg/dL) 73.86 ± 6.16
- C4 (mg/dL) 14.65 ± 5.56
- CR (mg/dL) 0.90 ± 0.15
- AST (mg/dL) 19.21 ± 8.27
- ALT (mg/dL) 22.13 ± 6.97
- ESR (mm/hr) 51.60 ± 3.60
- Anti-dsDNA (IU/mL) 62.83 ± 10.64
- SLEDAI 4.30 ± 2.28
- Prednisolone (mg/d) 8.36 ± 3.16

During the study, the accountability of returned drug in the experimental group was 15.02% and in the control group was 14.11%. After 6 months of add-on therapy, the serum level of AST in the experimental group improved significantly (p = 0.04) (Table 3). In addition, there was no significant change in the serum level of AST in the normal range. However, there was no significant change in the serum level of AST after 6 months of therapy. The frequency of returned drug was 89% (21/23) in the experimental group and 86% (20/23) in the control group. The frequency of returned drug between the experimental and control groups was not significantly different.

**Discussion**

After 6 months of therapy, there was a mild increase of the serum level of AST in the experimental group (p = 0.102) (Table 3), but the serum level of AST was still in the normal range. However, there was no significant change in the serum level of AST after 6 months of therapy in the normal range. However, there was no significant change in the serum level of AST in the experimental group (p = 0.123). The first double-blind randomized controlled trial using TCM add-on therapy to taper steroid dose while concurrently preventing disease flare-up was conducted in this study. The frequency of returned drug was 89% (21/23) in the experimental group and 86% (20/23) in the control group. The frequency of returned drug between the experimental and control groups was not significantly different.

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less than the 13% (3/23) in the control group. There was one very severe flare-up resulting in the admission of a patient in the control group who suffered two flare-ups during the study period, but there was none in the experimental group. Although the incidence of flare-ups did not reach statistical significance between the two groups, a longer follow-up (1 year or more) in a future study may provide a more solid answer as to whether DCLWC can decrease the frequency of disease flare-up or not.

The safety of TCM therapy is a major concern to date. Some herbs, such as Aristolochia fangchi (known as "Guang Fang Ji" in Chinese medicine) and Aristolochia manshuriensis (known as "Guan Mutong" in Chinese medicine) have been reported to cause renal toxicity [23]; however, no herbs used in DCLWC have been reported to cause renal toxicity. After 6 months of observation, DCLWC was shown to be really safe and without renal toxicity. Although AST was slightly elevated in the experimental group, it was still within the normal range. However, a further work-up is mandatory to ensure the safety of DCLWC in relation to the liver.

One clinical trial has been conducted using TCM in SLE patients. It was reported that the Liuwei Dihuang pill can improve the therapeutic effectiveness and counteract the adverse effects of steroid and immunosuppressive agents in the treatment of SLE, and reduce the recurrence of the disease [24]. There were several drawbacks of the study: first, it lacked of double-blind design; second, there was a lack of disease activity scores before and after treatment; and third, the steroid dose was tapered by schedule, despite the disease activity of SLE.

In conclusion, add-on therapy of DCLWC to the conventional therapy for the treatment of SLE was safe and might have a borderline effect on decreasing disease activity, but it was unable to assist in tapering the dosage of steroid after 6 months of clinical trial. However, long-term follow-up and large-scale studies are necessary in the future.

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