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ORIGINAL ARTICLE

The efficacy and safety of total glucosides of peony in the treatment of primary Sjögren's syndrome: a multi-center, randomized, double-blinded, placebo-controlled clinical trial

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Abstract

To evaluate the efficacy and safety of total glucosides of peony (TGP) in adults with primary Sjögren's syndrome (pSS). A multi-center, randomized, double-blinded, placebo-controlled study was conducted between March 2012 and July 2014 at ten Chinese hospitals. In total, 320 pSS patients—classified according to the 2002 American-European Consensus Group Criteria—were randomized (2:1 ratio) to receive TGP(600 mg, tid) in the TGP group or placebo for 24 weeks in the placebo group. Study personnel, investigators, and patients were blinded to the treatment grouping. The primary endpoint was the improvement of EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) at week 24. The secondary endpoints were dry eyes/mouth/skin/nose/throat/vagina visual analogue scale (VAS), pain and discomfort VAS, fatigue VAS, mental discomfort VAS, patient global assessment (PGA), EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), Schirmer's test, basal/stimulated salivary flow-rate values, and erythrocyte sedimentation rate (ESR). All adverse events were recorded during the trial period. ESSPRI improved more in the TGP than the placebo group ($p < 0.001$). Dry eyes/throat/vagina VAS, fatigue VAS, mental discomfort VAS, PGA, Schirmer's test, and ESR also improved more in the TGP group than in the placebo group (all $p < 0.05$). Stimulated salivary flow-rate values increased in the TGP group at week 12 but not at week 24. Adverse events in TGP group were 10.9%. TGP can alleviate some dryness symptoms as well as disease activity in pSS patients over 24 weeks. TGP was well tolerated by study subjects. TGP seems to be an effective and safe treatment for pSS.

Keywords Randomized controlled trials · Sjögren's syndrome · Total glucosides of peony

Xia Liu and Xiaomei Li contributed equally to this work.

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Introduction

Sjögren's syndrome (SS) is a systemic autoimmune disease characterized by dryness of the eyes and mouth [1]. SS is a highly prevalent rheumatologic disease that is predominant in females [2]. Around a third of SS patients have extraglandular systemic involvement, and SS patients with evidence of other autoimmune rheumatic disease are classified as secondary SS, while those without are considered to have primary SS (pSS) [3]. The pathology of the disease is not completely understood, but chronic inflammatory infiltration in the exocrine glands is the pathological hallmark of pSS. Production of inflammatory cytokines also increases. IL-17 has been shown to be a dominant cytokine linked to immunopathogenesis in the minor salivary glands of pSS patients and plays a role in corneal barrier disruption in murine models [4, 5]. Moreover, Th17 cells play a critical role in the pathogenesis of experimental Sjögren's syndrome [6].

Current treatments mainly include supplemental treatments and systemic treatments. Pilocarpine, cevimeline, 0.05% cyclosporin A eye drops, and 0.1% fluorometholone eye drops can improve symptoms and tear secretion, and nebulized isotonic saline can improve the vocal production of SS patients [2, 7–9]. However, glucocorticoids and immunosuppressants—such as methotrexate (MTX), leflunomide (LEF), and hydroxychloroquine (HCQ)—or biological agents did not improve symptoms of dryness in patients with pSS [10–12]. In addition, evidence supporting the use of disease-modifying drugs is limited. Recent studies have shown that the effects of MTX on dry eyes and dry mouth are not fully known [10], and that HCQ is ineffective at treating dry mouth [11]. LEF, azathioprine, and mycophenolate mofetil all had no effect on dry mouth or dry eyes [13–15]. Cyclophosphamide, corticosteroids, and other immunosuppressants are used more to address organ involvement. As for biological agents, rituximab was observed to be effective for treating extraglandular manifestations in uncontrolled studies and to have a modest effect on SS symptoms [16], but a randomized, placebo-controlled, parallel-group trial indicated that rituximab had no effect on the variables associated with dryness [11]. A recent study suggested that EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) decreased significantly during abatacept treatment but increased post-treatment. Moreover, salivary and lacrimal gland function did not change during treatment [17]. The BELISS open-label phase II study suggested that belimumab did not change salivary flow rates or Schirmer's test results for pSS patients [18]. Actually, these immunosuppressants are used to address the extraglandular manifestations of pSS as well as organ-specific involvement. In addition to the uncertainty regarding efficacy, adverse effects may also occur in patients using immunosuppressants and biological drugs.

Paeonia lactiflora pall (also called the "Chinese peony") has a long history of use in Chinese medicine for the treatment of various diseases, such as rheumatoid arthritis and systemic lupus erythematosus [19]. Total glucosides of peony (TGP) are extracted from the root of the *Paeonia lactiflora* pall. In 1998, TGP was approved by the Chinese State Food and Drug Administration for the treatment of rheumatoid arthritis. TGP has been demonstrated to have immunomodulatory effects. In previous studies, TGP inhibited dendritic cell maturation and function by selectively blocking TLR4/5 activation, sequentially leading to the impairment of Th1 and Th17 differentiation and of associated cytokines in vivo. This impairment, in turn, led to anti-inflammatory and anti-rheumatic effects [20, 21]. In non-obese diabetic (NOD) mouse models, TGP has been demonstrated to be effective in delaying the onset of Sjögren's syndrome-like disease [22]. Moreover, TGP might improve the saliva secretion of salivary glands and pathological damage of submandibular glands by upregulating AQP-5 and its mRNA expression in submandibular glands [23]. Open trials have demonstrated that TGP is effective at improving saliva and tear flow rates and reducing inflammatory markers [24, 25]. A pilot randomized controlled trial on a small study sample suggested that TGP would also be beneficial in the treatment of SS [26]. However, no systematic, large scale, randomized controlled study has been conducted on the effect of TGP on pSS.

The purpose of this multi-center, randomized, double-blinded, placebo-controlled clinical trial was to evaluate the efficacy and safety of TGP in the treatment of pSS.

Materials and methods

Patients

This multi-center, double-blinded, randomized, placebo-controlled trial recruited patients between March 2012 and July 2014 from ten hospitals in China to evaluate the efficacy and safety of TGP. This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Review Board of China-Japan Friendship Hospital (approval number 2012-14). Approval was also obtained from Tianjin Medical University General Hospital, Xi-Jing Hospital, Anhui Medical University Affiliated Provincial Hospital, The First Affiliated Hospital of Bengbu Medical College, and The First Affiliated Hospital of Nanjing Medical University. All subjects provided written informed consent for participation before study enrollment. The protocol was registered on the Chinese Clinical Trial Registry (ChiCTR-TRC-12002325).

Study subjects were considered for inclusion in the study if they fulfilled the inclusion criteria: (1) diagnosed with pSS according to the 2002 American-European Consensus Group international classification criteria for pSS [3]; (2) newly

diagnosed or had previously been treated; (3) between 18 and 75 years old; (4) with symptoms of dry eyes and dry mouth; and (5) autoantibody positive (ANA or anti-SSA or anti-SSB or RF), and/or erythrocyte sedimentation rate (ESR) > 25 mm/h, and/or hypergammaglobulinemia.

Exclusion criteria included (1) pregnancy (including pre-pregnant and lactating women); (2) stimulated salivary flow rates less than 0.15 mL/min; (3) active liver disease or evidence of abnormal liver function (ALT, AST, and TBIL more than 1.5 times the upper limit of normal); (4) impaired renal function (serum creatinine ≥ 133 mmol/L or 1.5 mg/dL); (5) patients with neutrophil levels less than 3.0×10^9/L, severe anemia (hemoglobin less than 80 g/L), or platelet counts less than 80×10^9/L; or (7) any other chronic disease evidence of significant extra-glandular manifestations. Subjects were not permitted to use immunosuppressive agents, corticosteroids, biological agents, or gland stimulators (glandular secretion agonists) within 3 months prior to enrollment.

Study design

Patients were randomly assigned to be treated either with oral TGP, in the TGP group, or with placebo, in the placebo group, in a 2:1 ratio. This ratio was used for ethical reasons, because we considered it likely that patients would benefit from the treatment. All study personnel, investigators, and patients remained blinded to the treatment group throughout the study, which was allowed in principle.

Randomization was achieved by computer-generated random allocation sequences prepared by the statistics department at Boon Pharmaceutical Research, Ltd., China. Drugs were uniformly packaged and distributed according to the random allocation sequence. The random coding was the unique identifier for each recruited patient. Each medication sample was distributed with an emergency note as decode. The randomization key was sealed separately in duplicate and given to the relevant clinical trial and statistical entities. After the end of the study, the blind was removed by statistical analysts, researchers, and staff who had access to the randomization key. All patients received the same dosage of TGP or placebo, 600 mg, tid.

The TGP capsule was 0.3 g and contained glucosides of peony no less than 104 mg. The capsule was provided by Ningbo Lansen Pharmaceutical Co. Ltd. Ningbo, China. The dose was two capsules twice or three times a day. As the efficacy might be associated with dose to a certain degree, and the incidence of adverse effects was also likely to correlate to the dose (including soft stools and increased number of defecation), the dose was designed as two capsules twice a day for the first week, and increased to two capsules three times a day, which was in accordance with the manufacturer's instructions.

Outcomes

The primary endpoint was ESSPRI at week 24. The secondary endpoints were based on dry eye/mouth/skin/nose/throat/vagina visual analogue scale (VAS) scores, pain discomfort VAS score, mental discomfort VAS score, fatigue VAS score, and patient global assessment (PGA) (normal–severe, 0–10) at each follow-up. Schirmer's test values, basal salivary flow rate values, stimulated salivary flow rate values, and EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) were evaluated at weeks 12 and 24. ESR values and serum immunoglobulin (IgG, IgA, and IgM) levels were also measured at each follow-up.

Each follow-up examination was undertaken in the outpatient departments, at weeks 4/8/12/18/24 ± 5 days. There were some differences among follow-up examinations, some measurements were recorded every time; however, some measurements were only recorded at baseline, week 12 and week 24.

All adverse events were recorded at each visit from baseline to week 24. These included any symptom, syndrome, or disease that affected the health of patients and occurred during the observation process, including any situation discovered by laboratory analysis or other diagnostic process, such as unplanned measures that needed to be undertaken, leading to exit from research, or abnormal results found by laboratory examination with clinical significance. The severity criteria of adverse effects were classified as follows: mild: the symptom and sign could be perceived by patients but were tolerable and did not affect their daily lives. Moderate: uncomfortable and the patient's daily life was affected; however, their daily activities were not affected. Severe: the patient's daily activities were affected and were not conducted.

Statistical analysis

The sample size was calculated based on previous studies that the efficacy of TGP was 50%, and the efficacy of placebo was 20 to 30%, $\alpha = 0.05$ and $\beta = 0.2$; the number of patients in the treatment group was 174 and the placebo group was 87. Considering the complex nature of clinical practice, a total of 300 patients were recruited (200:100 for treatment and placebo), which exceeded the calculated number. Data were analyzed as intent to treat. All randomly assigned patients who did not withdraw before the first treatment were included in the efficacy analysis. Missing data for the primary end point were treated by last observation carried forward (LOCF). Study data was captured through an Electronic Data Capture Boon EDC®, and source data and was verified by the study coordinator(s). Data were presented as mean (standard deviation (SD), range). SAS version 9.3 (SAS Institute, Cary, North Carolina) was used for statistical analyses. A normal distribution was not assumed, and therefore, the Wilcoxon rank sum test was used for statistical analysis. The two-sided Wilcoxon

signed rank test was used for intra-group change from baseline analysis and Wilcoxon rank sum test was used for inter-group comparisons. p values less than 0.05 were considered statistically significant. As for ESSPRI and the other VAS scores, we used Bonferroni method for multiple comparisons, p values less than 0.01 were considered statistically significant.

Results

Baseline characteristics

Three hundred twenty patients with pSS were screened at ten hospitals, and 314 patients were eligible to participate in the study and were randomly assigned to either the TGP group or the placebo group. In total, 211 patients received TGP treatment and 103 patients received the same dose of placebo. The data analysis set was the full analysis set, and the rate of missed follow-up was less than 20%. The patients who discontinued were due to adverse events, which occurred more often in the TGP group and were mainly gastrointestinal adverse reactions (Fig. 1). Baseline characteristics of the two groups were similar (Table 1).

Efficacy

1. *ESSPRI*

The primary outcome was the difference of ESSPRI at week 24 from baseline. ESSPRI of the TGP and placebo group declined from 3.30 (SD 1.89) and 3.09 (SD 1.77) to 2.57 (SD 1.80) and 2.66 (SD 1.80) at week 24, respectively (Fig. 2a). Improvement of the TGP group as shown by the decrease of ESSPRI from baseline was significantly higher than that of the placebo group at week 24 ($p < 0.001$).

2. *VAS scores*

Figure 2b and Supplementary Fig. 1 show dry eye VAS and fatigue VAS, and PGA of the TGP group were significantly improved compared with those of the placebo group at weeks 24 ($p = 0.001$, $p < 0.001$ $p = 0.004$, respectively). The significant differences were found in dry mouth VAS, dry throat VAS, dry vagina VAS, and mental discomfort VAS between the two groups at week 24 ($p = 0.019$, $p = 0.027$, $p = 0.022$, $p = 0.018$, respectively), nevertheless, the differences were no longer significant after Bonferroni correction.

3. *Schirmer's test*

Figure 3 shows that Schirmer's test results for tear secretion of the left and right eyes exhibited an increasing trend at weeks 12 and 24. The increase of the Schirmer's test results of the TGP and placebo group were 1.17 (SD 6.57) and 0.63 (SD 7.02) at weeks 12, respectively and 3.09 (SD 6.58) and 1.06 (SD 5.54) at week 24, respectively. There was a significant difference between the two groups at week 24 ($p = 0.034$).

4. *Salivary flow rate*

Obvious changes in basal salivary flow rate after treatment were not observed in either the TGP or placebo group at weeks 12 and 24. However, the increase of stimulated salivary flow rate of the TGP and placebo groups were 0.09 (SD 0.37) and 0.04 (SD 0.42) at week 12, respectively and 0.17 (SD 0.40) and 0.12 (SD 0.40) at week 24, respectively. The improvements of the TGP group were significantly higher than those of the placebo group at week 12 ($p = 0.027$). However, no significant difference was shown between the two groups at week 24 ($p = 0.083$) (Fig. 4).

5. *ESSDAI scores*

There are 12 items in ESSDAI, but as this study included only milder pSS patients without severe organ involvement, only three domains (constitutional, lymphadenopathy, and glandular) of the ESSDAI were covered here. There were no significant differences between the ESSDAI scores of the TGP and placebo groups at any of the follow-up points (data not shown).

6. *IgG*

The TGP group experienced significant decreases in IgG levels from baseline levels. Serum IgG levels at baseline, week 12 and week 24, were 21.4 g/L (SD 5.8), 19.1 g/L (SD 5.0), and 19.8 g/L (SD 5.8), respectively. Decreases in IgG were − 2.1 g/L (SD 7.3) and − 1.1 g/L (SD 4.0) at weeks 12 and 24, respectively. There were no significant differences between the magnitudes of the IgG decreases of the two groups. In addition, serum IgA and IgM levels after treatment had not obviously improved by weeks 12 and 24 (data not shown).

7. *ESR*

At week 24, ESR of the TGP group and placebo group decreased from 39.6 (SD,18.9) and 36.8 (SD 20.3) to 29.6 (SD,15.9) and 34.0 (SD 19.3). ESR was significantly decreased in TGP group compared with placebo group at week 24 ($p = 0.016$).

8. *Adverse events*

Table 2 reports all adverse events that occurred during this trial. There were 23 patients (10.9%) who reported adverse

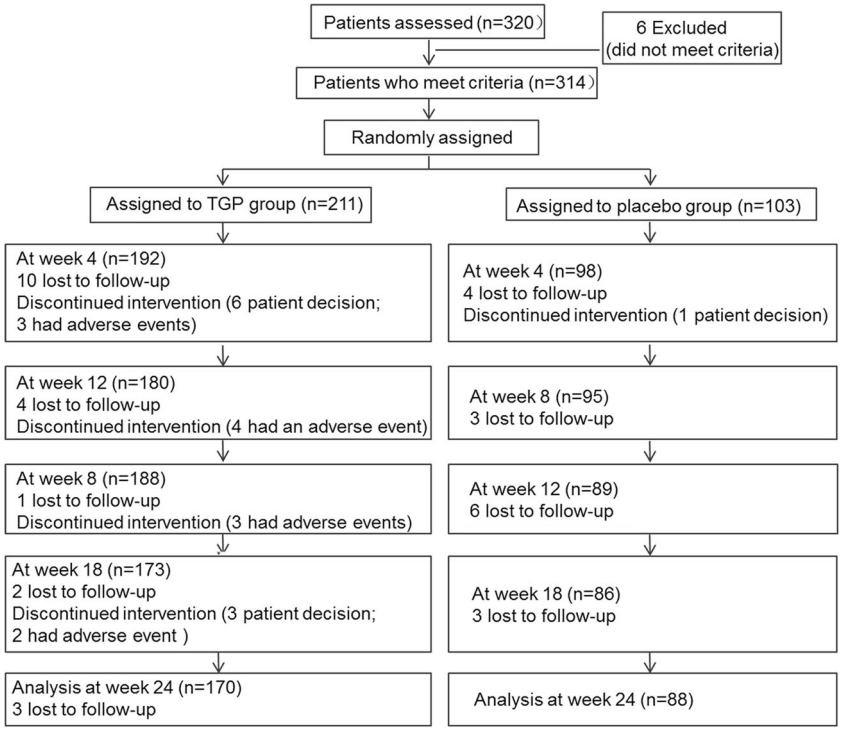

Fig. 1 Flow chart of the study of TGP for treatment of primary Sjögren's syndrome. A total of 320 patients were assessed, and 314 patients were randomized: 211 to TGP and 103 to placebo group. At week 24, 170 patients in TGP and 88 patients in placebo group completed the study

events in the TGP group, and 3 patients (2.9%) reported adverse events in the placebo group. In the TGP group, the adverse events reported by 12 patients were considered to be related to the TGP treatment. Adverse reactions to TGP included gastrointestinal discomfort and diarrhea. Among these 12 patients, two patients discontinued TGP use due to intolerance. In addition, 10 patients discontinued TGP use due to other adverse reactions unrelated to TGP treatment. No severe adverse events were observed during the study.

Table 1 Baseline characteristics

Characteristic	TGP ($n = 211$)	Placebo ($n = 103$)	p value
Mean (SD) age, years	48.9 (12.2)	47.5 (11.3)	0.339
Mean(SD) time since diagnosis, years	36.0 (59.7)	36.1 (41.4)	0.984
Women, *n* (%)	205 (97.2)	96 (93.2)	0.343
Mean(SD) ESSPRI score	3.30 (1.88)	3.10 (1.77)	0.403
Mean(SD) dryness VAS score (0–10)			
Eyes	4.93 (2.49)	4.87 (2.32)	0.682
Mouth	5.77 (2.36)	5.55 (2.22)	0.476
Nose	2.41 (2.58)	2.47 (2.53)	0.692
Throat	3.06 (2.94)	2.78 (2.75)	0.543
Skin	2.77 (2.64)	2.83 (2.43)	0.556
Vagina	2.25 (2.73)	1.93 (2.54)	0.355
Mean(SD) pain discomfort VAS score (0–10)	3.11 (2.45)	2.89 (2.40)	0.451
Mean(SD) fatigue discomfort VAS score (0–10)	3.25 (2.31)	2.99 (2.27)	0.342
Mean(SD) mental discomfort VAS score (0–10)	2.64 (2.27)	2.53 (2.40)	0.557
Mean(SD) PGA VAS score (0–10)	4.56 (1.95)	4.48 (1.63)	0.77
Mean(SD) Schirmer's test result, mm	10.47 (7.00)	9.36 (5.69)	0.566
Mean(SD) basal salivary flow rate, mL/min	0.36 (0.31)	0.39 (0.37)	0.703
Mean(SD) stimulated salivary flow rate, mL/min	1.05 (0.61)	1.08 (0.59)	0.556
Mean(SD) ESR, mm/h	39.6 (18.9)	36.8 (20.3)	0.158
Mean(SD) immunoglobulin level (IgG), g/L	21.4 (5.8)	21.7 (5.1)	0.413

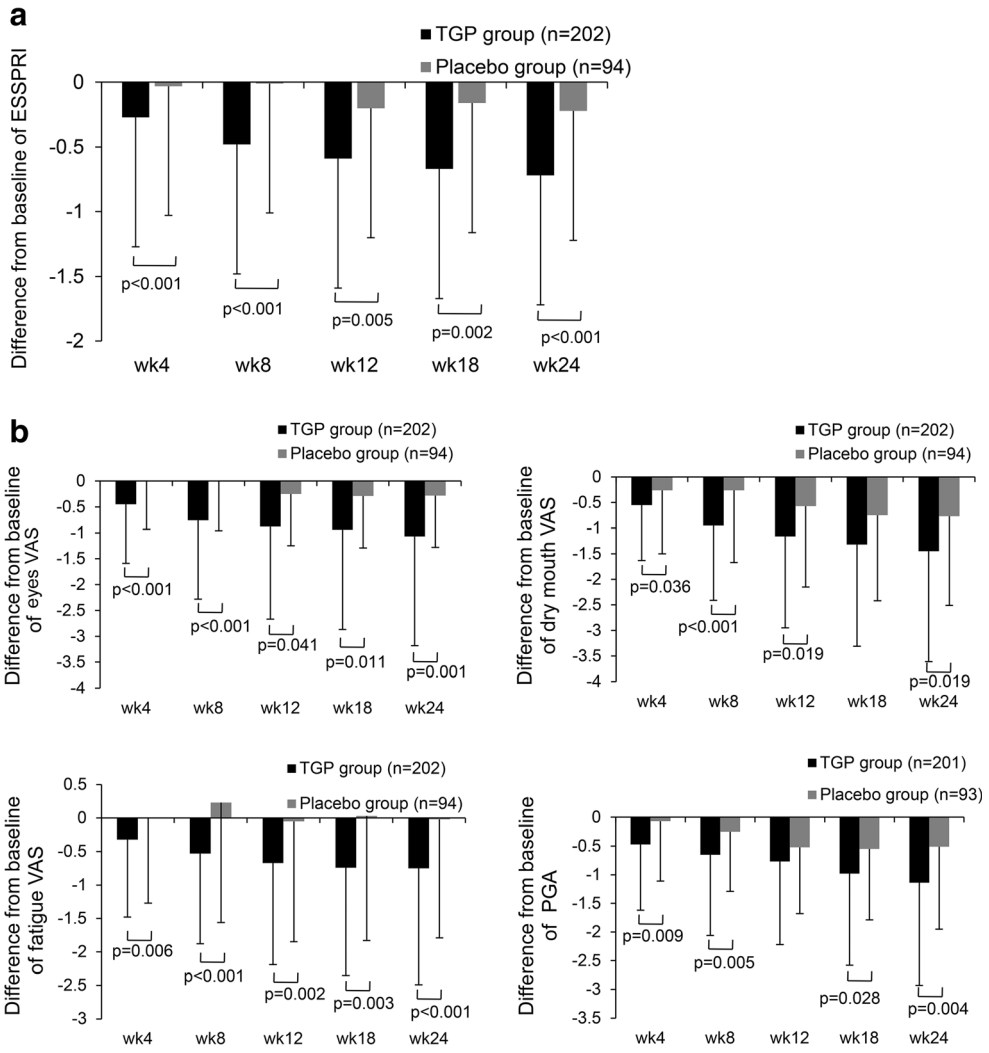

Fig. 2 **a** Difference from baseline (△) in ESSRPI at weeks 4, 8, 12, 18, and 24. $p < 0.01$ is considered significant after Bonferroni adjustment between TGP and placebo groups. **b** Difference from baseline in dry eyes VAS, dry mouth VAS, fatigue VAS, and PGA at weeks 4, 8, 12, 18, and 24. $p < 0.01$ is considered significant after Bonferroni adjustment between TGP and placebo groups

Discussion

In this study, we focused on pSS patients who did not exhibit significant extra-glandular manifestations to observe the efficacy and safety of TGP for the treatment of pSS. The results show that ESSPRI scores improved dramatically. TGP treatment significantly alleviated some dryness symptoms and also improved fatigue and PGA during this 24-week trial. Tear secretion showed a good improvement, and stimulated salivary flow rate increased to some extent. The TGP safety

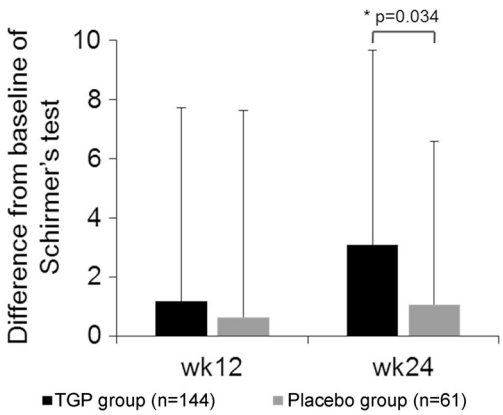

Fig. 3 Comparison of difference from baseline in Schirmer's test at weeks 12 and 24 between TGP and placebo groups; * $p < 0.05$

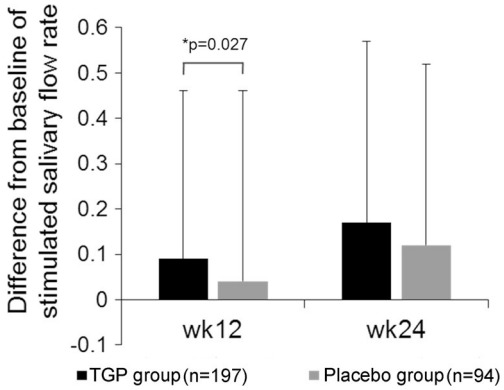

Fig. 4 Comparison of difference from baseline in stimulated salivary flow rate at weeks 12 and 24 between TGP and placebo groups; * $p < 0.05$

Table 2 Adverse events during the 24-week study period

Variable	Patients, *n* (%)	
	TGP (*n* = 211)	Placebo (*n* = 103)
Adverse event		
Gastrointestinal discomfort	2 (0.95)	
Diarrhea	10 (4.74)	1 (0.97)
Abnormal liver function	3 (1.42)	1 (0.97)
Leukopenia	1 (0.47)	
Thrombocytopenia	1 (0.47)	
Skin ulcer	1 (0.47)	
Allergies, skin rash		1 (0.97)
Hypergammaglobulinemia	1 (0.47)	
Skin purpura	1 (0.47)	
Ovarian cyst	1 (0.47)	
Renal colic	1 (0.47)	
Renal calculus	1 (0.47)	
Total events	23 (10.9)	3 (2.9)

profile was well accepted. All these results suggest that TGP has an obvious therapeutic effect on mild-to-moderate pSS, at least during a 24-week course of therapy.

Symptomatic treatments are currently the main approach for the treatment of pSS, but the results of these treatments have so far been disappointing and novel treatments are needed [27]. A pilot study suggested that TGP may be a beneficial treatment for pSS, but found no difference in ESSPRI between treatment and placebo groups; however, there was a difference in stimulated and unstimulated salivary flow rates [26]. We observed that ESSPRI of the TGP group had significantly improved not only at week 24, but also at each follow-up compared with those of the placebo group in this 24-week study. Furthermore, eye dryness symptoms of the TGP group were significantly improved at all follow-up points, and improved at weeks 8 and 24 after Bonferroni correction. In addition, tear secretion of the TGP group had increased significantly compared with that of the placebo group at week 24, according to Schirmer's test results. There were no obvious changes in the basal salivary flow rates of either group. However, significant differences were observed in the stimulated salivary flow rates between the two groups at week 12. Moreover, throat dryness symptoms lightened at weeks 4 and 8. Mouth and skin dryness symptoms also had a tendency of improvement. Previous study has also demonstrated that TGP could improve the patient's sleep, appetite, physical strength, and other general conditions, to significantly improve the quality of life of patients [28]. In our study, we also found fatigue symptoms had greatly relieved during all trial period. PGA had decreased at several follow-up points including week 24. These results suggest that TGP alleviates some dryness and discomfort symptoms.

In addition, IgG levels had decreased after TGP treatment, but there was no significant difference between the two groups. In this study, ESR was obviously decreased in the TGP group at week 24. This finding suggests that TGP has an effect on the inflammation resulting from pSS.

TGP has been used in clinical practice for more than 10 years, and its adverse effects were mild. Previous study reported the incidence of adverse effects was 14.3% [28]. The main adverse effects were gastrointestinal reactions and diarrhea. These adverse effects could be relieved after continuous administration in most patients, and in some patients, these could be remitted by dosage reduction or drug withdrawal. The same results were observed in our study. Adverse events in TGP group was 10.9%, and the main adverse event was diarrhea at a rate of 4.8%. No serious adverse effects recorded, and the patients tolerated TGP treatment well.

There are some limitations to this research. Firstly, pathologic change is a gold standard in diagnosis and disease activity. However, a pathologic study was not performed before or after treatment in this study. Secondly, SS is a chronic disease and requires long-term treatment. The observation period of this study was 24 weeks, and a longer follow-up study should be performed to ensure that TGP can offer long-term benefits for pSS patients. Further study should involve longer observation periods and explore the mechanism of action of TGP in SS.

This first multi-center, randomized, double-blinded, placebo-controlled clinical study confirms that TGP is effective, safe, and well-tolerated in the treatment of pSS.

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Source(s) of support None.

Compliance with ethical standards

Conflict of interests All authors declare that they have no conflicts of interest.

References

1. Youinou P, Pers JO (2015) Primary Sjogren's syndrome at a glance today. Joint Bone Spine 82(2):75–76. https://doi.org/10.1016/j.jbspin.2014.10.018
2. Ramos-Casals M, Tzioufas AG, Stone JH, Siso A, Bosch X (2010) Treatment of primary Sjogren syndrome: a systematic review. JAMA 304(4):452–460. https://doi.org/10.1001/jama.2010.1014
3. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, Daniels TE, Fox PC, Fox RI, Kassan SS, Pillemer SR, Talal N, Weisman MH (2002) Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 61(6):554–558

4. Katsifis GE, Rekka S, Moutsopoulos NM, Pillemer S, Wahl SM (2009) Systemic and local interleukin-17 and linked cytokines associated with Sjogren's syndrome immunopathogenesis. Am J Pathol 175(3):1167–1177. https://doi.org/10.2353/ajpath.2009.090319
5. De Paiva CS, Chotikavanich S, Pangelinan SB, Pitcher JD, 3rd, Fang B, Zheng X, Ma P, Farley WJ, Siemasko KF, Niederkorn JY, Stern ME, Li DQ, Pflugfelder SC (2009) IL-17 disrupts corneal barrier following desiccating stress. Mucosal Immunol 2 (3):243–253. doi:https://doi.org/10.1038/mi.2009.5
6. Lin X, Rui K, Deng J, Tian J, Wang X, Wang S, Ko KH, Jiao Z, Chan VS, Lau CS, Cao X, Lu L (2015) Th17 cells play a critical role in the development of experimental Sjogren's syndrome. Ann Rheum Dis 74(6):1302–1310. https://doi.org/10.1136/annrheumdis-2013-204584
7. Deveci H, Kobak S (2014) The efficacy of topical 0.05% cyclosporine A in patients with dry eye disease associated with Sjogren's syndrome. Int Ophthalmol 34(5):1043–1048. https://doi.org/10.1007/s10792-014-9901-4
8. Lin T, Gong L (2015) Topical fluorometholone treatment for ocular dryness in patients with Sjogren syndrome: a randomized clinical trial in China. Medicine (Baltimore) 94(7):e551. https://doi.org/10.1097/md.0000000000000551
9. Tanner K, Nissen SL, Merrill RM, Miner A, Channell RW, Miller KL, Elstad M, Kendall KA, Roy N (2015) Nebulized isotonic saline improves voice production in Sjogren's syndrome. Laryngoscope 125(10):2333–2340. https://doi.org/10.1002/lary.25239
10. Skopouli FN, Jagiello P, Tsifetaki N, Moutsopoulos HM (1996) Methotrexate in primary Sjogren's syndrome. Clin Exp Rheumatol 14(5):555–558
11. Gottenberg JE, Ravaud P, Puechal X, Le Guern V, Sibilia J, Goeb V, Larroche C, Dubost JJ, Rist S, Saraux A, Devauchelle-Pensec V, Morel J, Hayem G, Hatron P, Perdriger A, Sene D, Zarnitsky C, Batouche D, Furlan V, Benessiano J, Perrodeau E, Seror R, Mariette X (2014) Effects of hydroxychloroquine on symptomatic improvement in primary Sjogren syndrome: the JOQUER randomized clinical trial. JAMA 312(3):249–258. https://doi.org/10.1001/jama.2014.7682
12. Devauchelle-Pensec V, Mariette X, Jousse-Joulin S, Berthelot JM, Perdriger A, Puechal X, Le Guern V, Sibilia J, Gottenberg JE, Chiche L, Hachulla E, Hatron PY, Goeb V, Hayem G, Morel J, Zarnitsky C, Dubost JJ, Pers JO, Nowak E, Saraux A (2014) Treatment of primary Sjogren syndrome with rituximab: a randomized trial. Ann Intern Med 160(4):233–242. https://doi.org/10.7326/m13-1085
13. van Woerkom JM, Kruize AA, Geenen R, van Roon EN, Goldschmeding R, Verstappen SM, van Roon JA, Bijlsma JW (2007) Safety and efficacy of leflunomide in primary Sjogren's syndrome: a phase II pilot study. Ann Rheum Dis 66(8):1026–1032. https://doi.org/10.1136/ard.2006.060905
14. Price EJ, Rigby SP, Clancy U, Venables PJ (1998) A double blind placebo controlled trial of azathioprine in the treatment of primary Sjogren's syndrome. J Rheumatol 25(5):896–899
15. Willeke P, Schluter B, Becker H, Schotte H, Domschke W, Gaubitz M (2007) Mycophenolate sodium treatment in patients with primary Sjogren syndrome: a pilot trial. Arthritis Res Ther 9(6):R115. https://doi.org/10.1186/ar2322
16. Atzeni F, Doria A, Turiel M, Sarzi-Puttini P (2007) What is the role of rituximab in the treatment of rheumatoid arthritis? Autoimmun Rev 6(8):553–558. https://doi.org/10.1016/j.autrev.2007.02.004
17. Meiners PM, Vissink A, Kroese FG, Spijkervet FK, Smitt-Kamminga NS, Abdulahad WH, Bulthuis-Kuiper J, Brouwer E, Arends S, Bootsma H (2014) Abatacept treatment reduces disease activity in early primary Sjogren's syndrome (open-label proof of concept ASAP study). Ann Rheum Dis 73(7):1393–1396. https://doi.org/10.1136/annrheumdis-2013-204653
18. De Vita S, Quartuccio L, Seror R, Salvin S, Ravaud P, Fabris M, Nocturne G, Gandolfo S, Isola M, Mariette X (2015) Efficacy and safety of belimumab given for 12 months in primary Sjogren's syndrome: the BELISS open-label phase II study. Rheumatology (Oxford) 54 (12):2249–2256. doi:https://doi.org/10.1093/rheumatology/kev257
19. He DY, Dai SM (2011) Anti-inflammatory and immunomodulatory effects of paeonia lactiflora pall., a traditional chinese herbal medicine. Front Pharmacol 2:10. https://doi.org/10.3389/fphar.2011.00010
20. Zhou Z, Lin J, Huo R, Huang W, Zhang J, Wang L, Sun Y, Shen B, Li N (2012) Total glucosides of paeony attenuated functional maturation of dendritic cells via blocking TLR4/5 signaling in vivo. Int Immunopharmacol 14(3):275–282. https://doi.org/10.1016/j.intimp.2012.07.012
21. Lin J, Xiao L, Ouyang G, Shen Y, Huo R, Zhou Z, Sun Y, Zhu X, Zhang J, Shen B, Li N (2012) Total glucosides of paeony inhibits Th1/Th17 cells via decreasing dendritic cells activation in rheumatoid arthritis. Cell Immunol 280(2):156–163. https://doi.org/10.1016/j.cellimm.2012.12.005
22. Li CL, He J, Li ZG, Zheng LW, H. H (2013) Effects of total glucosides of paeony for delaying onset of Sjogren's syndrome: an animal study. J Craniomaxillofac Surg 41 (7):610–615. doi:https://doi.org/10.1016/j.jcms.2012.11.042
23. Wu GL, Pu XH, Yu GY, Li TY (2015) Effects of total glucosides of peony on AQP-5 and its mRNA expression in submandibular glands of NOD mice with Sjogren's syndrome. Eur Rev Med Pharmacol Sci 19(1):173–178
24. Li XM, Li XP, Wang GS, Qian L, Wang W (2006) Effectiveness and safety of total glucosides of peony in the treatment of patients with Sjögren syndrome. Anhui Medical Journal 27:370–371
25. Zhang HF, Hou P, Xiao WG (2007) Clinical observation on effect of total glucosides of paeony in treating patients with non-systemic involved Sjogren syndrome. Zhongguo Zhong Xi Yi Jie He Za Zhi 27(7):596–598
26. Zhou Y, Jin L, Kong F, Zhang H, Fang X, Chen Z, Wang G, Li X, Li X (2016) Clinical and immunological consequences of total glucosides of paeony treatment in Sjogren's syndrome: a randomized controlled pilot trial. Int Immunopharmacol 39:314–319. https://doi.org/10.1016/j.intimp.2016.08.006
27. Barone F, Colafrancesco S (2016) Sjogren's syndrome: from pathogenesis to novel therapeutic targets. Clin Exp Rheumatol 34(4 Suppl 98):58–62
28. Lu J, Yang PT, Shen H, Xiao WG, Zhao LJ (2006) Clinical application of total glucosides of paeony in Sjogren syndrome. J Chin Med Univ 35(5):522–524