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Clinical trial

The clinical efficacy and safety of oral compound glycyrrhizin in adult patients with mild-to-moderate active alopecia areata: A randomized controlled study

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ABSTRACT

Introduction: The efficacy of the current therapy for alopecia areata (AA) remains unsatisfactory, due to disease recurrence and drug side effects. This study was designed to evaluate the clinical efficacy, recurrence rate, and safety of the new therapy with oral glycyrrhizin in adult patients with mild to moderate active AA.

Methods: This was a randomized controlled trial using two oral tablets of 25 mg glycyrrhizin three times per day (tid) for test group (65 patients), or two oral tablets of 25 mg cystine tid for the control (56 cases). Patients in both groups were also treated with topical 0.05% halometasone cream twice daily (bid). The treatment period was 24 weeks, including 12 weeks of active therapy, followed by another 12 weeks of observation.

Results: The complete regrowth rate and total efficacy of the test group were significantly higher than the control group (16.92% vs. 5.36%, and 63.08% vs. 30.36%, $p < 0.05$). In particular, the total efficacy in glycyrrhizin-treated moderate or short-duration patients was significantly higher than the control (53.33% vs. 11.11%, and 72.70% vs. 26.47%, $p < 0.05$). During the follow-up period, the recurrence rate was 12.3% (8/65) in the test group, lower than that of the control. The incidence rate of adverse effects between the two groups was not statistically different (9.23% vs.10.71%, $p > 0.05$), and no severe adverse events were observed.

Conclusions: Glycyrrhizin treatment is safe and effective for adult patients with mild to moderate active AA. This therapy has higher therapeutic efficacy in patients with moderate AA or short duration of the disease.

1. Introduction

Alopecia areata (AA) is characterized by the sudden onset of hair loss in patients. AA presents typically as well-circumscribed round or oval patches without the presence of inflammation or scarring. Approximately half of all AA patients have recurrent disease. It can progress into alopecia totalis (AT)in severe cases, which involves the entire scalp, or alopecia universalis (AU), an advanced form of AA that is systemic and involves the whole body [1]. The incidence of AA is approximately 0.1-0.2% [2], with slight differences among different populations. In China, the incidence of AA is relatively higher,at0.20-0.27% [3].While AA does not endanger the lives of patients, the disease may impact the mental health [4]and negatively affect the quality of life of patients [4,5].

The etiology and pathogenesis of AA remain to be fully elucidated. Currently, AA is known to be an organ-specific autoimmune disease because hair follicles are targeted by T lymphocytes. AA is also associated with neuropsychological factors as well as endocrine and genetic factors [6]. Although there are numerous treatment options available for AA patients, none of them are curative [7].

The AA treatment guidelines recommend the use of topical and local corticosteroids, topical minoxidil, and contact immunotherapy for patients with mild-to-moderate AA with an area of alopecia less than 50%.In some patients with active AA, the disease begins small but

Abbreviations: AA, alopecia areata; AT, alopecia totalis; AU, alopecia universalis; t.i.d., three times per day; b.i.d., twice per day; JAK, janus kinase; ACTH, adrenocorticotropic hormone; 11-HSD2, 11-beta-hydrosteroid dehydrogenase; 3MGA, 3-monoglucuronyl-glycyrrhetinic acid; SALT, severity of alopecia tool; TE, total efficacy; PPS, per protocol set; TLRs, toll-like receptors

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enlarges rapidly, which makes it difficult to treat with topical medications alone [8]. For these cases, systemic corticosteroids and Janus kinase (JAK) inhibitors [9,10] have been used successfully in the clinic, but these therapies are not highly recommended as a first-line treatment due to their adverse effects and associated risks, such as increased susceptibility to infection. Therefore, it is necessary to develop safer and more effective systemic drugs to support the current AA treatment options.

Although orally-administered glycyrrhizin has been widely used in China for many years to treat AA [11,12];however, it has not been well reported due to the lack of clinical evidence. As we know, glycyrrhizin is found in the licorice root of a small leguminous shrub, known as Glycyrrhizaglabra L. During metabolism by intestinal bacteria after oral ingestion, glycyrrhizin is hydrolyzed into two pentacyclic triterpenoids, which are stereoisomers: 18α- and 18β-glycyrrhetinic acids. 18β-glycyrrhetic acid is similar to the adrenocorticotropic hormone (ACTH) in chemical structure, and it displays a strong affinity for liver 5β-reductase in the steroid hormone metabolism. Therefore, 18β-glycyrrhizic acid and its derivatives exhibit a remarkable broad spectrum of biological and pharmacological activities, including antitumor, anti-inflammatory, antioxidant, antiviral, antimicrobial, antiulcer, anti-diabetes, hepatoprotective, cardioprotective and neuroprotective effects [13].Glycyrrhizin also shows obvious pharmacological benefits for the treatment of AA with minor adverse effects, including hypertension, hypokalemia, and pseudo-aldosteronism. Moreover, licorice-induced pseudo-aldosteronismis caused by the inhibition of type 2 11 beta-hydrosteroid dehydrogenase (11β-HSD2), leading to the accumulation of cortisol in tubular epithelial cells, by which mineral corticoid receptors are activated to induce the excretion of potassium and hypokalemia. In addition, circulating glycyrrhizic acid is metabolized in the liver to become 3-monoglucuronyl-glycyrrhetinic acid (3MGA) that may be a genuine causative agent for licorice-induced pseudo-aldosteronism. When licorice is used, 3MGA in the plasma or urine could function as a marker compound to prevent adverse effects [14].

Previous studies showed that short-term system use of corticosteroids for AA can control the progress of the disease, but relapse rates after this treatment were as high as 25–85% [15,16].On the other hand, long-term systemic treatment with glucocorticoids also brings many side effects. Considering the shortcomings of the systemic use of glucocorticoids, we designed a short-term system use of oral compound glycyrrhizin for AA treatment, to explore whether this novel therapy can control disease progression, reduce the recurrence rate, and limit the risk of medication. In this study, a randomized, controlled clinical trial was conducted to evaluate the efficacy, recurrence rate and safety of oral compound glycyrrhizin for the treatment of adult patients with mild to moderate active AA.

Alopecia areata (AA) is characterized by the sudden onset of hair loss in patients. AA presents typically as well-circumscribed round or oval patches without the presence of inflammation or scarring. Approximately half of all AA patients have recurrent disease. It can progress into alopecia totalis (AT)in severe cases, which involves the entire scalp, or alopecia universalis (AU), an advanced form of AA that is systemic and involves the whole body [1]. The incidence of AA is approximately 0.1-0.2% [2], with slight differences among different populations. In China, the incidence of AA is relatively higher,at0.20-0.27% [3].While AA does not endanger the lives of patients, the disease may impact the mental health [4]and negatively affect the quality of life of patients [4,5]. The etiology and pathogenesis of AA remain to be fully elucidated. CurrentlyAA is known to be an organ-specific autoimmune disease because hair follicles are targeted by T lymphocytes. AA is also associated with neuropsychological factors as well as endocrine and genetic factors [6]. Although there are numerous treatment options available for AA patients, none of them are curative [7].; The AA treatment guidelines recommend the use of topical and local corticosteroidstopical minoxidil, and contact immunotherapy for patients with mild-to-moderate AA with an area of alopecia less than 50%.In some patients with active AA, the disease begins small but enlarges rapidly, which makes it difficult to treat with topical medications alone [8]. For these cases, systemic corticosteroids and Janus kinase (JAK) inhibitors [9,10] have been used successfully in the clinic, but these therapies are not highly recommended as a first-line treatment due to their adverse effects and associated risks, such as increased susceptibility to infection. Therefore, it is necessary to develop safer and more effective systemic drugs to support the current AA treatment options.

2. Methods

2.1. Study design

This project is a randomized and controlled clinical trial, which was carried out at a single research center (Huashan Hospital, Shanghai, China) between January 2016 and December 2016.

All patients meeting the inclusion criteria and who met the definitive diagnosis criteria for AA were recruited by two professional hair disease specialists, and randomly allocated to the control group or the test group with a 1:1 allocation ratio.

The period of treatment was 24 weeks, including 12 weeks of active therapy, followed by another 12 weeks of observation (followed-up). All the recruited patients were assessed at baseline, at 12^{th}week (the end of active treatment) and 24^{th} week (the end of follow-up). This study design is summarized in Fig.1.

The study was approved by the Ethics Committee of Huashan Hospital (Shanghai, China), and registered as a clinical trial (ChiCTR1800018691). All recruited patients provided written informed consent.

2.2. Recruitment strategies

Many patients with alopecia visited the hair specialist clinic of the Department of Dermatology of Huashan Hospital every day. All recruited patients in this study were from the hair specialist clinic, as mentioned above. A total of 135 adult patients with mild to moderate active AA were initially diagnosed and recruited at the hair specialist clinic between January 2016 and December 2016. The team members of this study which names are in the list of authors are responsible for the procedure of treatment, collection of data, and monitoring follow-up.

2.3. Participants

The sample size was calculated based on information of a reported study [11].The parameters will be set as follows: $\alpha = 0.05$,power $(1-\beta) = 0.9$, mean difference = -0.341, standard deviation (SD) = 1. Thus, the current clinical trial needed 86 participants. Accordingly, 90 participants were recruited according to our protocol plan, 45 in the test group and 45 in the control group. However, considering the possible loss of the subjects during the period (considering at least 10% dropout rate according to usual practice), a cohort of 135 subjects were finally recruited, of which 68 participants were randomized into the test group and other 67 into the control group.

Disease severity was evaluated according to the Severity of Alopecia Tool (SALT)scoring system [1], which included: S_0 = no hair loss; S1 = < 25% hair loss; S2 = 25–49% hair loss; S3 = 50–74% hair loss; S4 = 75–99% hair loss; and S5 = 100% hair loss. In our study, S1 was defined as mild AA and S2 as moderate AA.

Disease activity includes two states: (1) active disease, which indicated a positive hair-pull test, hair loss continued to expand, or the appearance of new alopecia patches; and (2) non-active disease, which indicated a negative hair-pull test, no new alopecia patches observed for one month, and a small amount of vellus growth.

The inclusion criteria for this study included:(1) verified AA diagnosis;(2) presented with patchy AA;(3) area of alopecia of < 50%;(4)

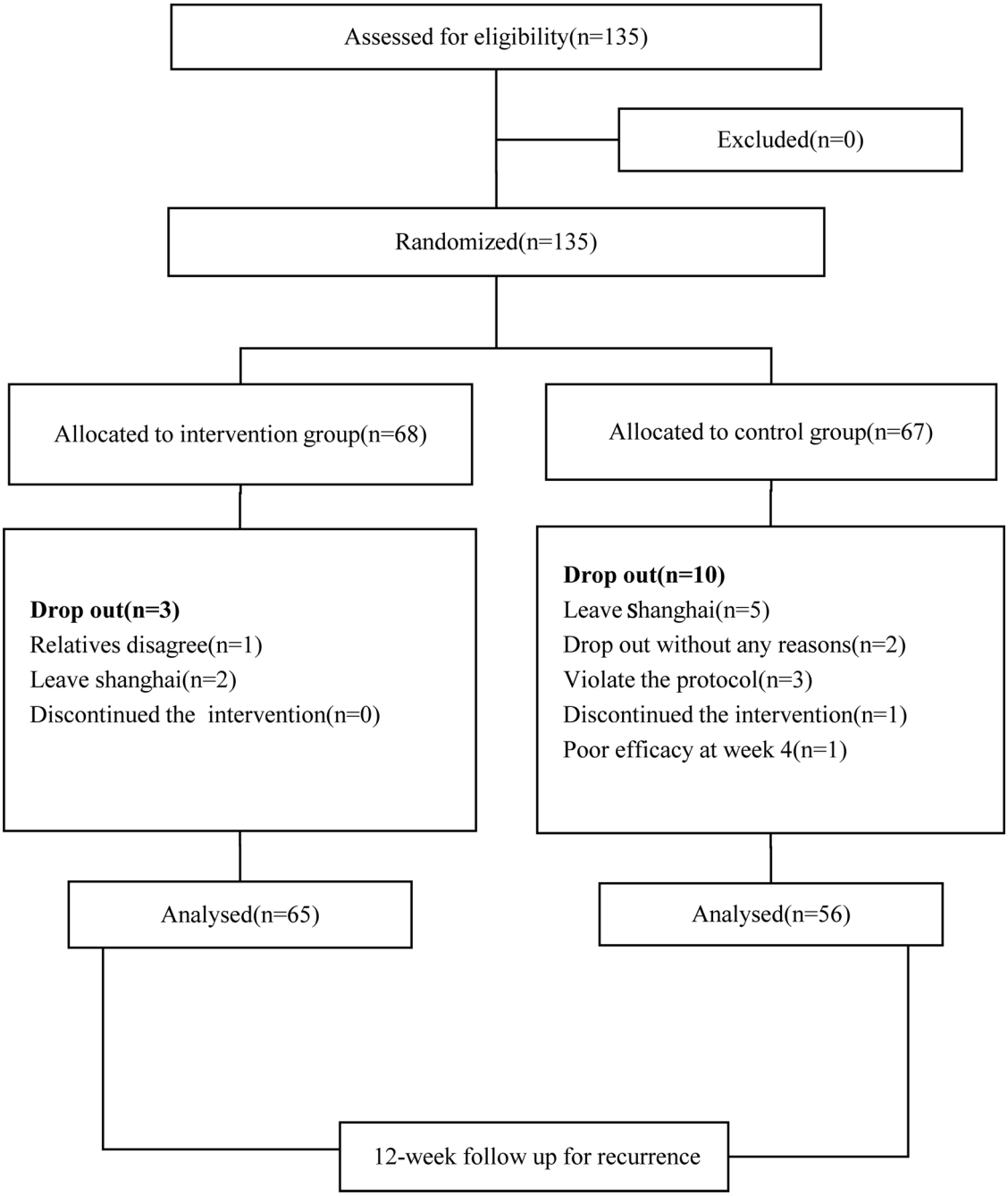

Fig. 1. Flowchart of participants in the study.

positive hair-pull test; and (5) 18–65 years old.

The exclusion criteria included: (1) area of alopecia of ≥50%;(2) ophiasis AA;(3) negative hair-pull test;(4)history of allergy or contraindication to glycyrrhizin;(5) pregnant or nursing;(6) history of immunodeficiency systemic diseases;(7) other active inflammatory or autoimmune skin diseases;(8)received systemic corticosteroids, glycyrrhizin, or other biological agents within the previous 4 weeks; or (9) received topical/local injection of corticosteroids, topical minoxidil, or contact immunotherapy treatment within one week.

2.4. Randomization and allocation

Two professional hair specialists were responsible for registering general information about all the participants and completing the baseline assessments. An independent statistician who did not participate in this study generated a list of random numbers by the SPSS 22.0(IBM, Chicago, IL, USA). When the randomized table was created, the randomized sequence was hidden in sealed envelopes. After each participant completed the baseline assessment, an independent staff member not involved in the trial opened the envelopes in front of the participants in the order. Then, based on the random sequence, participants were assigned to the control or test group. Other four hair specialists were responsible for follow-up work of all participants in the subsequent 12^{th}week and 24^{th}week. The statistician and all the hair specialists were blind to allocation and treatments.

2.5. Blinding

The test group and the control group used two different drugs to treat alopecia areata. Two types of drugs were packed in the same

plastic containers with a specific number, but no difference in appearance between them. Before each container with the drug was opened, everybody (including the participants, the investigators, and statistician) was blinded to the assignment and treatment. However, when the containers were opened by patients at home, some of the participants may recognize the medication which they had previously been prescribed. In return, this study was a single-blind trial.

This study also used the secondary unblinding method. After the end of the trial, all of the data were secured. The treatment groups corresponding to each case were differentiated by group A or B, and the statistician analyzed the data to obtain a summary report. Subsequently, the second unblinding was carried out to reveal which group was the test group and which group was the control group, and the clinical trial results were further analyzed.

2.6. Interventions

Patients in the test group were administered two oral tablets of 25 mg compound glycyrrhizin (Meineng, Minophagen Pharmaceutical Co., Ltd. of Japan, Batch Number:J20130077) tid, while patients in the control group received two oral tablets of 25 mgcystine (Cystine Tablets, Shanxi Luohe Pharmaceutical Co., Ltd., Shan Xi, China, Batch Number:H20073289) tid. Patients in both groups received local treatment with 0.05%halometasonetopical cream (Aoneng, Bright Future Pharmaceutical Laboratories Limited, Hong Kong, China, Batch Number: HC20150049) bid.

2.7. Parameters

The parameters included clinical efficacy, recurrence rate, and safety analysis. The assessment of clinical efficacy was conducted by the examination of the extent and density of hair re-growth according to the SALT scores. There were four categories complete regrowth, effective, improved, and ineffective, (1) The complete regrowth indicated that all alopecia areas showed terminal hair growth, and the hair-pull test was negative; (2) The effective indicated that most areas showed vellus hair growth, terminal hair covered > 50%,and the hair-pull test was negative; (3) The improved indicated that most areas showed vellus hair growth, terminal hair coverage rate was < 50%, and the hair-pull test was negative; and (4) The ineffective indicated that little vellus hair growth had occurred, hair continued to fall out, and the hair-pull test was positive during the three-month treatment observation.

The total efficacy (TE) was determined by the following formulaTE = (number of complete regrowth cases + number of effective cases) / the total number of cases evaluated × 100%

At the 24th week of the treatment, the follow-up of patients was performed by phone call. The status of hair loss was divided into the complete regrowth (no hair loss), the improvement (hair loss of better than the baseline) and the recurrence (hair loss of more than 20% as compared with baseline). If the patients reported recurrence, they were asked to assess the status of hair by a professional dermatologist in a nearby clinic. We used the confirmed results as a final follow-up result. According to the information obtained from the follow-up, the recurrence rate was determined by the number of recurrent cases / the total number of cases evaluated × 100%

Safety analysis was monitored before and after treatment by clinical observation and laboratory tests, including complete blood counts, biochemistry profile (including Na, K, calcium, BUN, creatinine, and liver function tests) and muscle enzyme test. At the end of the follow-up, the patients were asked to self-test blood pressure and record it. The adverse effects were also counted. Accordingly, the incidence rate of adverse effects was calculated by the cases of adverse effects/total cases × 100%.

2.8. Statistical analysis

Statistical analysis was performed using the principle of per-protocol set (PPS) data analysis. The *t*-test was used for comparisons of measurement data, while the Chi-square test was used for categorical data. The exact probability test was used for indices that failed to meet the conditions of the Chi-square test. A *p*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 22.0(IBM, Chicago, IL, USA).

3. Results

3.1. Patient characteristics

Fig. 1 showed the flow of patients through the study. Three patients in the test group were lost to follow-up. One patient was forced to withdraw because of disagreement between of the relatives of the patient, and two patients could not continue because they left Shanghai. In the control group, one patient terminated the treatment during week 4, due to poor efficacy (ineffective), and another ten patients were lost to follow-up. Two patients had no reason to withdraw, five patients left Shanghai, and three patients violated the treatment protocol. There was a difference in the drop-out rate between groups, which may be related to some of the patients knowing they were taking the control drug. Finally, a total of 121 eligible patients completed the study with a dropout rate of 10.37%. Moreover, no participant dropped out due to adverse effects.

Table 1 showed the demographic information of patients. A total of 68 males and 67 females were recruited with an average age of 42.93 ± 13.83 years and average disease duration of 3.40 ± 3.48 months. There were 99 patients (73.33%) with mild AA and 36 patients (26.67%) with moderate AA. No significant differences were observed between the test and control groups with regard to gender, age, disease duration, or disease severity (all $p > 0.05$).

3.2. Clinical efficacy

As shown in Fig. 2, the complete regrowth rate and total efficacy (TE) in the test group were significantly higher than those in the control group (16.92% vs. 5.36%, 63.08% vs. 30.36%, $p < 0.05$), but the ineffective rate of the test group was lower than the control (6.15% vs.32.14%, $p < 0.05$). However, the effective and improved rates between the two groups were not statistically different.

As shown in Table 2, the TE of mild AA was higher than that of

Table 1
Comparison of the baseline characteristics between the two groups.

Characteristics	Test group (n = 68)	Control group (n = 67)	Total (n = 135)	*p*-value
Completed trial	65(95.59%)	56(83.58%)	121(89.63)	
Male	35(51.47%)	33(49.25%)	68(50.37%)	> 0.05
Female	33(48.53%)	34(50.75%)	67(49.63%)	
Age (mean ± SD years)	44.07 ± 13.76	41.77 ± 13.90	42.93 ± 13.83	> 0.05
Duration (mean ± SD months)	3.29 ± 3.59	3.51 ± 3.43	3.40 ± 3.48	> 0.05
Mild (S1)	53(77.94%)	46 (68.66%)	99(73.33%)	> 0.05
Moderate (S2)	15 (22.06%)	21 (31.34%)	36(26.67%)	

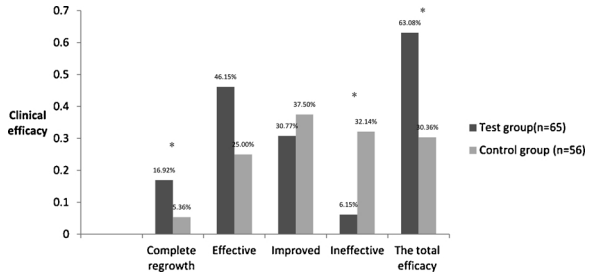

Fig. 2. Comparison of the clinical efficacy between the two groups. *$p < 0.05$.

moderate ones, regardless of the treatment (66.00% vs. 53.33%, 39.47% vs. 11.11%, $p < 0.05$). For mild AA, the complete regrowth rate and TE were higher in the test group than the control group (18.00% vs. 5.26%, 66.00% vs. 39.47%, $p < 0.05$). For moderate AA, the therapeutic effects were similar to mild AA, but the TE of the test group was significantly higher than that of the control group (53.33% vs.11.11%).

In the test group, the complete regrowth rate and TE of short-duration (< 3months) patients were higher than the long-duration (≥3 months) patients, but in the control group, there was no significant difference between the complete regrowth rate and TE. For short-duration patients, the complete regrowth rate and TE of the test group were higher than the control group, but for long-duration patients, no significant difference was found between the two groups.

3.3. Recurrence rate

The recurrence rate was determined at the end of the period of followed-up. In the test group, nine patients had the complete regrowth, 48 patients were found the improvement, and eight patients (12.3%) experienced a relapse during the observation period of 12 weeks. While in the control group, five patients had the complete regrowth, 38 patients were found the improvement, and 13 patients (23.2%) experienced a relapse.

3.4. Adverse effects

None of the recruited patients developed severe adverse effects in this study. As shown in Table 3, there were six patients (9.23%) with adverse reactions in the test group, including three cases of mild edema of the lower extremities, 1 case of increased blood pressure, and two cases of scalp itching. Among the three patients with lower extremities edema, two were female (35 years old with moderate AA and 52 years old with mild AA); one was male (45 years old with moderate AA).The 35-year-old female patient had a history of lower extremities edema after standing for a long period, which was relieved spontaneously after a break. The other two patients had no history of lower extremities edema. The mild edema was visible to the investigator during the physical examination, yet there were no patient complaints. One patient with elevated blood pressure was a female, 55 years old, with mild AA and no history of hypertension. Her blood pressure increased from 130/90 mmHg (before enrollment) to 150/90 mmHg (after four weeks of treatment), although this patient had no discomfort. All these patients were advised to consume a light diet. Their symptoms resolved within two weeks of discontinuing the drug. No other severe conditions, such as hypokalemia, decrease in muscle strength, or cardiac symptoms, were observed in the recruited patients. Furthermore, in the control group, there were 6(10.71%) patients with adverse reactions, including three cases of scalp folliculitis, 2 cases of reduced appetite, and 1 case of insomnia. In these patients, scalp folliculitis was improved by one week after drug discontinuation, and treatment was resumed after the scalp folliculitis had resolved. The other symptoms resolved spontaneously within two weeks after drug discontinuation. There was no statistically different from the incidence rate of adverse effects between two groups. There were no abnormal changes in lab tests (complete blood counts, biochemistry profile, and muscle enzyme testing) in all of the recruited patients before and after treatment. During the follow-up period, all of the side effects related to therapy gradually subsided, and the blood pressure of all the recruited patients was found to be within normal levels.

4. Discussion

Although there are many therapies for AA, their efficacy remains unsatisfactory. Currently, the topical/local injection of corticosteroids or in combination with topical minoxidil is recommended for mild to moderate adult AA. However, many side effects of drugs exist, including skin atrophy, increased intraocular pressure, glaucoma, cataracts when the injection site is near the eye [17], as well as the appearance of folliculitis and telangiectasia. The efficiency of local hormone therapy in non-active AA is 18–62% [18–20], but this therapy may not effectively treat active AA that is rapid progressing [8]. The use of topical5% minoxidil is only effective in approximately 33% for patients with mild AA [21]. Therefore, there is a dire need for a safe and effective systemic therapy for mild to moderate active AA in the clinic.

The use of drugs derived from naturally occurring products is becoming increasingly popular worldwide. The oral compound glycyrrhizin is a preparation composed of glycyrrhizin, cysteine hydrochloride, and glycine, and its primary active component is glycyrrhizic acid, an active substance found in licorice. Glycyrrhizic acid has various immune-modulating activities and has long been used in the clinic as an anti-allergic and anti-inflammatory agents for many diseases, such as psoriasis vulgaris [22], active-stage generalized vitiligo [23],anaphylactoid purpura [24] and Riehl's melanosis [25]with remarkable therapeutic effects and few adverse effects.

Previously, glycyrrhizin was found to attenuate inflammatory responses induced by specific toll-like receptors (TLRs) in macrophages [26]. The anti-inflammatory effects of glycyrrhizin were specific for membrane-dependent receptor-mediated stimuli, suggesting that it's broad anti-inflammatory activity is mediated by its interaction with the lipid bilayer, thereby attenuating the receptor-mediated signaling, rather than blocking specific intracellular targets [26]. In China, the compound glycyrrhizin has been widely used to treat AA with high clinical efficacy [11,12]. However, it has not been mass-promoted

Table 2
Comparison of the clinical efficacy between the two groups with regard to disease severity and duration.

	Test group		Control group		*p*-value	*p'*-value
	Complete regrowth rate	Total efficacy	Complete regrowth rate	Total efficacy		
S1	9(18.00%)	33(66.0%)	2(5.26%)	15(39.47%)	< 0.05	< 0.05
S2	2(13.33%)	8(53.33%)	1(5.56%)	2(11.11%)	< 0.05	< 0.05
Duration (< 3 month)	8(24.24%)	24(72.7%)	1(2.94%)	9(26.47%)	< 0.05	< 0.05
Duration (≥3 month)	3(9.38%)	17(53.1%)	2(9.09%)	8(36.36%)	> 0.05	> 0.05

S1: < 25% hair loss; S2: 25–49% hair loss; *p*: comparison of the complete regrowth rate between the two groups; *p'*: comparison of the total efficacy between the two groups.

Table 3
Comparison of adverse reactions between the two groups.

Group	Adverse reactions	Edema	Increased blood pressure	Reduced appetite	Insomnia	Itchy scalp	Folliculitis
Test group(n = 65)	6(9.23%)	3(4.61%)	1(1.54%)	–	–	2 (3.08%)	–
Control group(n = 56)	6(10.71%)	–	–	2(3.57%)	1(1.79%)	–	3(5.36%)

because of lacking high-quality clinical evidence. This study is the first randomized, controlled trial to use the compound glycyrrhizin for treatment of mild to moderate active AA in adult patients. The clinical efficacy, recurrence rate, and safety of this therapy were evaluated in this study.

Our study demonstrated that compound glycyrrhizin could significantly increase the complete regrowth rate and TE in adult patients with mild to moderate active AA, suggesting this therapy can be used as a supplementary systemic therapy for AA patients.

Our study also found that compound glycyrrhizin increased TE in all recruited patients, especially in patients with moderate AA (53.33% vs. 11.11%). The clinical application of the compound glycyrrhizin will greatly benefit AA patients with poor outcomes of the existing treatments. Therefore, glycyrrhizin is recommended for patients with active and moderate AA.

Another finding in our study was that treatment with the compound glycyrrhizin could enhance the complete regrowth rate and the TE in patients with short durations(< 3months), but not in patients with long duration (≥ 3 months). Therefore, glycyrrhizin is highly recommended for AA patients with acute onset.

The recurrence rate in the test group during the period of follow-up was 12.3%, which was lower than that of the control group (23.2%), and also lower than that of the short-term system glucocorticoid therapies in previous reports [15,16].

After 12 weeks of treatment, approximately 9% of the participants in the test group had adverse reactions, which could be relieved by drug discontinuation. Our findings are consistent with the previous reports, which showed the treatment with 150 mg Glycyrrhizin compound per day orally for 3–6 months in the patients with vitiligo, Riehl's melanosis and alopecia areata was effective and well-tolerated. Another study also showed the incidence of adverse effects for the oral administration of the compound glycyrrhizin 75 mg/d in children over 12 months was 11.67% [12], indicating that glycyrrhizin is safe and well-tolerated in all patients.

Furthermore, this study may be biased toward patients with mild to moderate disease (< 50% scalp involvement). The small sample size and the short duration are limitations of this trial. Considering that the number of patients with moderate AA in this study was comparatively small (only 36 cases), an extended sample size should be of importance in future studies. Moreover, the follow-up period should also be extended to investigate recurrence conditions over a longer period of time.

5. Conclusions

In summary, the findings of our study revealed that oral compound glycyrrhizin is an effective therapy for adult patients with mild-to-moderate active AA. In particular, patients with moderate AA and patients with early-stage disease showed more benefits from this therapy.

Data availability

The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

Declaration of Competing Interest

There are no conflicts of interest and no no competing financial interests exist.

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