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Long-Term Efficacy of Tripterygium Hypoglaucum Hutch in Treating Patients with Behcet Disease-Associated Uveitis

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[&]Author Contribution:

Qiao DJ, Liu DM, and these author are contributed equally to this work.

Abbreviations:

ALT: Glutamic-pyruvic transaminase; AZA: Azathioprine; BCVA: Best corrected visual acuity; BD: Behçet disease; CIA: Collagen-induced arthritis; CME: Cystoid macular edema; Col: Colchicine; CsA: Cyclosporine A; CTX: Cyclophosphamide; ESI: Electrospray ionization; ESR: Erythrocyte sedimentation rate; FFA: Fundus fluorescein angiography; Foxp3: Fork head box Protein 3; FSH: Follicle-stimulating hormone; GVHD: Graft-versus-host disease; HIV: Human immunodeficiency virus; HPLC: High performance liquid chromatography; IFN-α: Interferon alpha; IL: Interleukin; LH: Luteinizing hormone mon month; OCT: Optical coherence tomography; Od: Right eye; Os: Left eye; THH: Tripterygium hypoglaucum Hutch; TwHF: Tripterygium wilfordii Hook F; TNF-α: Tumor necrosis factor alpha; yr: Year

1. Abstract

1.1. Background: Tripterygium Hypoglaucum Hutch (THH), extracts of a Chinese medicinal plant, shows immunosuppressive function and has been used in China for decades to treat autoimmune and inflammatory conditions. This retrospective study aimed to determine long-term efficacy of THH in treating patients with BD-associated uveitis.

1.2. Methods: Thirty-two patients with BD-associated uveitis resistant to conventional treatment were enrolled. Extracts of THH, 33mg/kg daily, were administered orally along with prednisone. The observation period was 46.8 months.

1.3. Results: A positive response to THH therapy was observed in 87.5% of patients, showing 62.5% complete remission of uveitis and 75.8% achieved visual acuity maintained or improvement. THH was effective to reduce the incidence of ocular relapse (from 2.9 to 0.4 per yr, $p<0.0001$) and the dose of corticosteroid (from 22.3 to 11.6 mg daily, $p<0.01$), with beneficial effects on extraocular manifestations. Side effects are rare and dose-dependent.

1.4. Conclusion: THH therapy has significant potential in treating patients with sight-threatening BD-associated uveitis, showing beneficial effects on improvement of visual acuity, long-term remission and extraocular lesions of BD.

2. Introduction

Behcet Disease (BD) is a chronic inflammatory disorder characterized by ocular, mucocutaneous, articular, vascular, gastrointestinal and central nervous system manifestations [1, 2]. As one of the most severe complications, BD-associated uveitis that is characterized by relapsing-remitting ocular inflammation results in irreversible retinal damage and vision loss, leading to 25% blindness in patients [3]. The goal for successful therapy in uveitis is to achieve sustained control of ocular inflammation and long-term remission to preserve vision. Up to date, the main stream of therapy for BD-associated uveitis is typically based on the use of corticosteroids and generalized immunosuppression regimens to promptly suppress ocular inflammation,

which are often poorly tolerated and associated with severe systemic adverse effects including cataracts, glaucoma, hypertension, diabetes, osteoporosis and increased risk of malignancies [3]. Therapy with biological agents may benefit a certain form of patients unresponsive to corticosteroids [4, 5]. However, their limited safety profile, high cost and poor compliance bring reluctance to physician. In particular, the high cost strongly restrict access to these therapies for patients in developing countries [6]. Therefore, there is an urgent need to seek for new agents that would efficiently control inflammation with less cost and minimized risk of adverse events, to avoid adversely affecting the quality of life in uveitis patients.

The Chinese medicinal plant Tripterygium Hypoglaucum Hutch (THH), known as "kun ming shan hai tang", is believed to have immunosuppressive, anti-inflammatory, antiallergic and antineoplastic activities [7]. Extracts of THH have been used in China for decades to treat autoimmune and inflammatory conditions. Small clinical trials suggest that THH may benefit patients with rheumatoid arthritis, lupus erythematosus, psoriasis vulgaris and chronic kidney disease [8-12]. Animal studies have revealed that THH as well as Tripterygium preparations have immunosuppressive effects on increasing survival rate and ameliorating inflammation in animal models of graft-versus-host disease (GVHD) [13] and collagen-induced arthritis (CIA) [14], without obvious hepatotoxicity and nephrotoxicity. Similar to THH and others from Tripterygium genus family, extracts of Tripterygium wilfordii Hook F (TwHF) have also shown therapeutic promise in treating rheumatoid arthritis [15-17]. THH shares multiple compounds with TwHF, including triptolide, tripterifordin, sesquiterpene alkaloid, catechin, celastrol, tannins and triterpenoid [18-20]. Among these elements, triptolide seems to be the most potent one for its immunosuppressive and anti-inflammatory capacities [21-24]. It has been reported that triptolide has immunosuppressive function in mouse model of experiment autoimmune uveitis (EAU) [25], an animal model that mimics human autoimmune uveitis, in which ocular inflammation is induced in rodents by active immunization with the retinal antigen, Interphotoreceptor Retinoid-Binding Protein (IRBP) in complete Freund's adjuvant (CFA) [26]. In mouse model of EAU, triptolide shows therapeutic effects comparable to CsA, the first line drug for the treatment of BD-associated uveitis [27]. Given the fact that extracts of THH have been widely prescribed in treating immunological disorders for centuries in China, there is surprisingly little know about the efficacy and safety of THH therapy for eye-specific autoimmunity, such as immune-mediated BD-associated uveitis.

In this manuscript, we carried out a retrospective study to determine the long-term efficacy and safety of THH therapy in treating patients with BD-associated uveitis, who were resistant to conventional immunosuppression treatment. Clinical outcomes were measured by the assessment of visual acuity, incidence of relapse, ocular and extraocular manifestations as well as adverse effects of the treatment. We demonstrate for the first time that THH treatment is beneficial to patients with BD-associated uveitis, showing improvement of visual acuity, long-term remission and minimized adverse events.

3. Methods

3.1. Ethical Approval

The study for THH therapy was ethically approved by the institutional review board of *** hospital, *** University and performed in anonymized patient records without informed consents required.

3.2. Study Design

Clinical records of 32 patients with active BD-associated uveitis, who were unresponsive to conventional treatment and referred to the Uveitis Clinic at *** hospital for therapeutic management with THH between 1998 and 2013, were retrospectively reviewed.

3.3. Patients and Entry Criteria

Thirty-two BD patients presenting active uveitis with a minimal follow-up of 2 years (yr) following THH treatment were included. All cases were diagnosed according to the standard criteria proposed by the Behçet Disease Research Committee and meet the diagnostic criteria of disease [28]. The clinical characteristics of patients were shown in (Table 1). Clinical and laboratory examinations were performed and analyzed in all patients prior to their inclusion into the study. Patients with evidence of blood abnormalities, liver function abnormalities, pregnancy, mental disorders and other serious systemic medical diseases were excluded.

3.4. Treatment Protocol

A washing period of at least 3 months (mon) was given prior to the initiation of THH therapy, in which immunosuppressants except for corticosteroids were discontinued to avoid the considerable antagonistic effects. Patients received oral THH extracts 33 mg/kg daily. The dose of oral prednisolone was 1-1.2 mg/kg daily, and then gently tapered down (10% per 1-2 weeks) to the maintenance dose of 5-15 mg daily, depending on the clinical activities of disease.

3.5. Clinical Assessment

Ophthalmologic and physical examinations was undertaken before and after THH therapy at a regular internal of 1-2 mon based upon disease activity and patients' response to treatment. The main outcome measures were Best-Corrected Visual Acuity (BCVA). The international uveitis scoring system was used to assess clinical activity of uveitis [29], such as cells and flares in anterior chamber, haze in vitreous, change of retinal vasculitis and Cystoid Macular Edema (CME), using slip lamp microscopy and binocular indirect ophthalmoscopy. Clinical response to THH therapy in patients were classified as the followings: (1) A complete resolution of ocular inflammation to zero and absence of relapse in the eyes within 2 yr of commencing treatment with THH was considered as a complete remission; (2) A partial remission was defined as an improvement of BCVA, a decrease of clinical disease activity and incidence of relapse (≤2 in 2-yr); (3) Patients showed partial resolution of ocular inflam-

mation and relatively high rate of relapse (>3 in 2-yr) were defined as non-responder to THH treatment. Extraocular manifestations and adverse events of THH therapy were also recorded.

3.6. Laboratory Assessment

Baseline assessment, including blood cell counts, Erythrocyte Sedimentation Rate (ESR), urinalysis, renal and liver function tests was performed in a regular interval. Chest X-ray was assessed routinely in patients to rule out tuberculosis. Fundus Fluorescein Angiography (FFA) was performed in all cases to confirm the changes in retinal vascultis and CME with Optical Coherence Tomography (OCT).

3.7. Statistical Analysis

Visual acuity and clinical response to THH therapy were analyzed by percentage for categorical variables. The changes in other ocular and extraocular manifestations in patients before and after the therapy were presented as Mean ± SD, and compared using the non-paired Mann-Whitney U test, one-way ANOVA test and Fisher's exact test, respectively. All statistical analysis was computed by using Prism 6 (GraphPad, California).

4. Results

4.1. The Clinical Characteristics of Patients

Thirty-two patients diagnosed as active BD-associated uveitis, who were resistant to conventional immunosuppression treatment, were enrolled in the study. The details of clinical characteristics of patients were shown in (Table 1). Twenty-five patients (78%) were male and 7 (22%) were female, with the average age of 30.8 ± 8.8 years (yr). Among the patients, 25 (78%) received a combined therapy of THH and corticosteroids, 3 (9.4%) received a combined therapy of THH, cyclosporine A (CsA) and corticosteroids, 2 (6.3%) received a combined therapy of THH, cyclophosphamide (CTX) and corticosteroids, and 2 (6.3%) for a combined therapy of THH, CTX, colchicine (Col) or azathioprine (AZA).

Table 1: Clinical characteristics and ocular manifestations

Patient No.	Gender	Age (yrs)	Previous Treatment	THH Therapy Duration (mon)	Ocular Manifestation	Macular Edema	
						Right eye	Left eye
1	F	37	CS	35	ou: panuveitis, retinal vasculitis	x	x
2	M	41	CS	42	ou: panuveitis, retinal vasculitis		
3	F	32	CS	25	ou: panuveitis, retinal vasculitis	x	x
4	M	16	CS	26	ou: panuveitis, retinal vasculitis	x	x
5	M	23	CS	82	ou: panuveitis, retinal vasculitis	x	x
6	F	30	CS	24	os: panuveitis, retinal vasculitis	x	x
7	M	37	CS	26	ou: panuveitis, retinal vasculitis		
8	M	24	CS	42	ou: panuveitis, retinal vasculitis		x
9	M	23	CS	80	ou: panuveitis, retinal vasculitis	x	x
10	M	31	CS	94	ou: panuveitis, retinal vasculitis	x	x
11	M	34	CS	43	ou: panuveitis, retinal vasculitis	x	x
12	M	17	CS	42	ou: panuveitis, retinal vasculitis	x	x
13	M	30	CS	50	ou: panuveitis, retinal vasculitis		
14	M	48	CS	62	ou: panuveitis, retinal vasculitis		
15	M	37	CS	26	ou: panuveitis, retinal vasculitis		
16	M	24	CS	33	ou: panuveitis, retinal vasculitis	x	x
17	M	15	CS	29	ou: panuveitis, retinal vasculitis	x	

18	F	36	CS	25	ou: panuveitis, retinal vasculitis		
19	M	15	CS	45	ou: panuveitis, retinal vasculitis	x	x
20	M	25	CS	46	ou: panuveitis, retinal vasculitis		
21	M	37	CS	30	od: panuveitis, retinal vasculitis	x	
22	F	23	CS	27	ou: panuveitis, retinal vasculitis		x
23	M	34	CS	162	ou: panuveitis, retinal vasculitis		
24	M	33	CS	34	ou: panuveitis, retinal vasculitis	x	x
25	M	30	CS	34	ou: panuveitis, retinal vasculitis	x	x
26	F	43	CS, CsA	117	ou: panuveitis, retinal vasculitis		
27	M	34	CS, CsA	33	ou: panuveitis, retinal vasculitis		
28	M	40	CS, CsA	27	ou: panuveitis, retinal vasculitis		
29	M	43	CS, CTX	25	ou: panuveitis, retinal vasculitis	x	x
30	F	46	CS, CTX	52	ou: panuveitis, retinal vasculitis		
31	M	26	CS, AZA	29	ou: panuveitis, retinal vasculitis		x
32	M	31	CS, CTX,Col	50	ou: panuveitis, retinal vasculitis	x	

AZA, azathioprine; Col, colchicine; CsA, cyclosporine A; CS, corticosteroids; CTX, cyclophosphamide; F, female; M, male; od, right eye; os, left eye; ou, both eyes; x, macular edema present.

4.2. Response of Ocular Manifestations

4.2.1. Visual Acuity: BCVA of 62 eyes in 32 patients were follow-up and evaluated for 2 yr. Changes in BCVA were defined as the followings: an increase of BCVA (≥2 lines), a decrease of BCVA (≤2 lines), and no change (change within 2 lines) [30]. Among these 62 eyes, 16 (25.8%) eyes showed an increase of BCVA and 31 (50%) eyes remained their visual acuity in response to THH therapy. Only 15 (24.2%) eyes had a decrease of BCVA due to severe secondary cataract occurred in 3 of these eyes (Table 2).

Table 2: Change in visual acuity in patients following THH treatment.

BCVA	No	%
Increase (≥2-line)	16	25.8
No change (between 2-line)	31	50.0
Decrease (≤2-line)	15	24.2

4.2.2. Relapse: Incidence of relapse of ocular inflammation was determined to evaluate the efficacy of THH treatment in patients. THH treatment significantly reduced the incidence of relapse from 2.9± 0.8 to 0.4 ± 0.5 within 2 yr ($p<0.01$; Figure 1). There were 11 (34.4%) patients received THH therapy, who claimed no recurrence of ocular inflammation during the entire period of observation.

4.2.3. Clinical Disease Activity: Clinical activity of uveitis, such as cells and flares in anterior chamber, haze in vitreous, change of retinal vasculitis and CME, were assessed in patients based upon the international uveitis scoring system [29]. THH therapy was effective to attenuate ocular inflammation, showing reduced disease score from 2.9 ± 2.1 to 0.8 ± 1.3 (Figure 2). A significant difference was detected in patients before and after THH therapy ($p<0.0001$). FFA detected a typical feather-like leakage of fluorescence in the retina of patients with active BD-associated uveitis. THH therapy resulted in a complete resolution of retinal vasculitis and fluorescence assessed by FFA in the same patient (Figure 3).

4.2.4. Clinical Response: A positive clinical response to THH therapy for BD-associated uveitis was observed in 28 (87.5%) patients ($p<0.0001$), including 20 (62.5%) with a complete remission (zero relapse in 2 yr) and 8 (25%) with a partial remission (≤2 relapses in 2 yr). Among the 32 patients received THH treatment, only 4 (12.5%) patients who showed partial resolution of ocular inflammation and relatively high rate of relapse (approximately 3-5 relapses in 2 yr) were defined as non-responder to THH therapy ($p=0.113$, (Figure 4)).

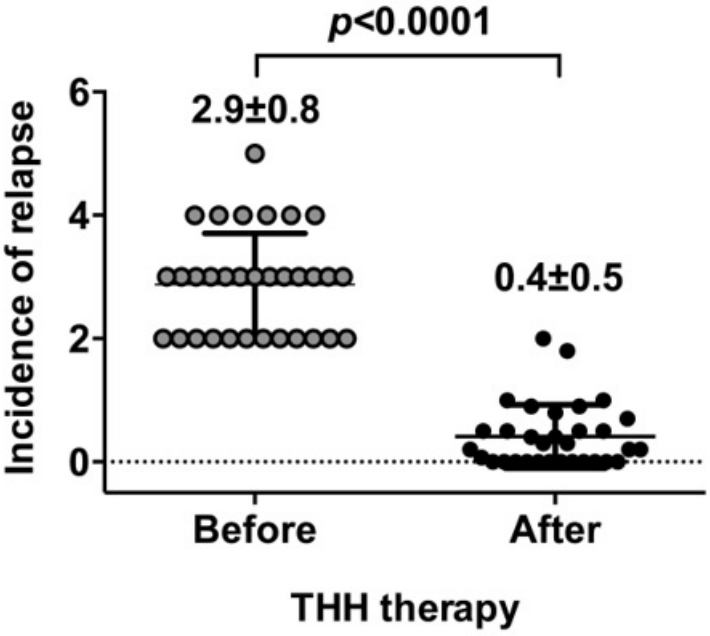

Figure 1: Incidence of ocular relapse (per yr) in patients with BD-associated uveitis before and after THH therapy. Data are presented as Mean ± SD. Each symbol represents one individual. ****, p<0.0001, non-paired Mann-Whitney U test.

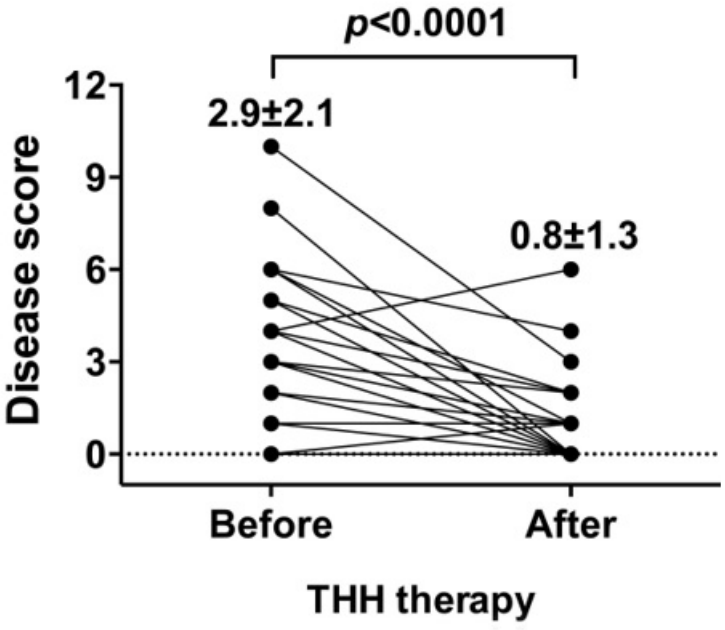

Figure 2: Clinical activity of uveitis assessed in patients with BD-associated uveitis before and after THH therapy. Data are presented as Mean ± SD. Each symbol represents one individual eye. ****, p<0.0001, the non-paired Mann-Whitney U test.

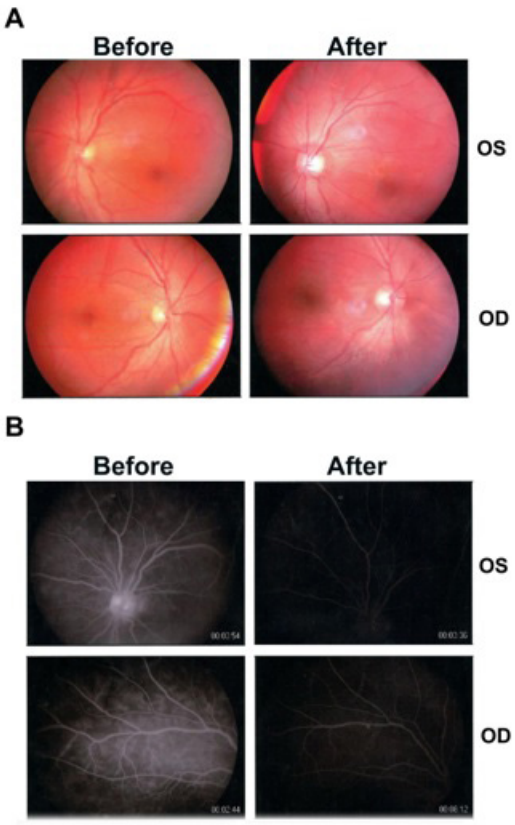

Figure 3: Fundus photographs and fundus fluorescein angiography (FFA) in one patient with BD-associated uveitis before and after THH treatment. A, Fundus of retinal lesions before (left) and after (right) THH therapy. B, Fundus fluorescein angiography frame with a typical BD-like leakage of fluorescence present in the midperiphery of eyes (left), which was completely disappeared after THH therapy (right).

Table 3: Extraocular manifestations in patients before and after THH therapy

	Before (no, %)		After (no, %)		P value	
Manifestations	Ever	Initial visit	1-yr	2-yr	1-yr	2-yr
Arthritis	8 (25)	6 (18.8)	2 (6.3)	1 (3.3)	0.257	0.104
Oral ulcer	32 (100)	21 (65.6)	8 (25)	1 (3.3)	0.002	<0.0001
Genital ulcer	20 (62.5)	14 (43.7)	4 (12.5)	0 (0.0)	0.011	<0.0001
Erythema nodosum	16 (50)	9 (28.1)	2 (6.3)	0 (0.0)	0.043	0.002
Papulopustule	13 (40.6)	10 (31.3)	4 (12.5)	0 (0.0)	0.129	0.0009

*p<0.05 for significant difference between the initial and 1-yr or 2-yr visits in patients received THH therapy, the Fisher's exact test.

4.3. Response of Extraocular Manifestations

Incidence of extraocular manifestations occurred in patients before and after the THH therapy was shown in (Table 3). Prior to the initiation of THH treatment, all patients with active BD claimed to have extraocular lesions, such as arthritis (50%), oral ulcer (100%), genital ulcer (65.6%), erythema nodosum (50%) and papulopustule (40.6%). BD patients received THH treatment for 1-yr showed large improvement of extraocular lesions in all aspects, with a significant difference detected in oral ulcer ($p<0.01$), genital ulcer and erythema nodosum ($p<0.05$). Moreover, 2-yr treatment with THH dramatically decreased the incidence of arthritis (from 18.8% to 3.3%) and oral ulcer (from 65.6% to 3.3%, $p<0.0001$) in patients with BD, and completely abolished the extraocular lesions of genital ulcer ($p<0.0001$), erythema nodosum ($p<0.01$) and papulopustule ($p<0.001$).

4.4. Dose of Corticosteroid

The dose of corticosteroid used in treating patients with BD-associated uveitis was analyzed before and after THH therapy (Figure 5). THH therapy was effective to attenuate ocular inflammation and reduced the daily use of corticosteroids from 22.3 ± 15.2 mg to 11.6 ± 5.45 mg. A significant difference was detected ($p<0.01$).

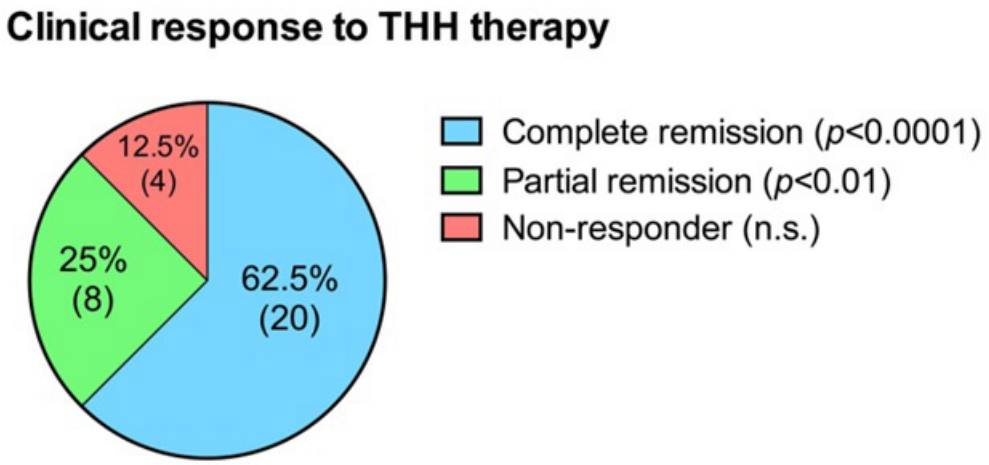

Figure 4: Clinical response to THH therapy over 2 yr in patients with active BD-associated uveitis. Data are presented as percentage and number of each group.

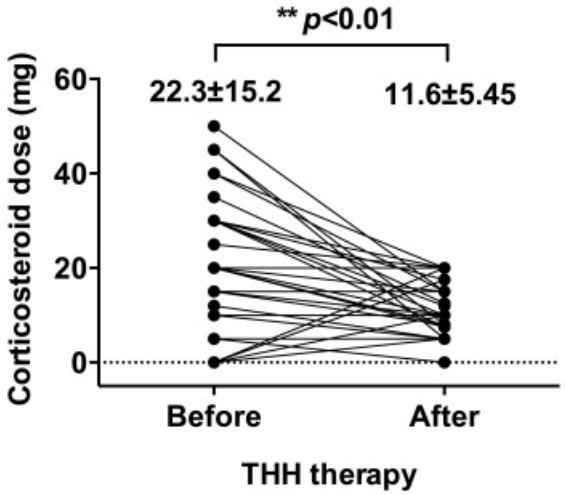

Figure 5: Dose of corticosteroid in treating patients with BD-associated uveitis before and after THH treatment. **, $p<0.01$, the non-paired Mann-Whitney U test

4.5. Side Effects

The main adverse effects occurred during the period of treatment were described in (Table 4). THH therapy was well tolerated in all patients. An increase of glutamic-pyruvic transaminase (ALT), total cholesterol and triglyceride was detected in 8 (25%), 5 (15.6%) and 8 (25%) patients, respectively. THH therapy resulted in irregular menstruation in females, showing oligomenorrhea and amenorrhea in 5 (71.4%) and 2 (28.6%) female patients, respectively.

These side effects could be resolved promptly while the THH dose was tapered down (from 33 to 21.6 mg/kg, daily). Infertility was not observed in male patients. No blood cell counts and renal abnormality were observed in all the cases during the period of observation (from 25 to 162 mon).

5. Discussion

Non-infectious uveitis, such as immune-mediated BD-associated uveitis, can be refractory to generalized immunosuppressive regimens and progressively leads to vision impairment and blindness [3]. Although immunotherapy with biological agents is beneficial to non-responder patients [4, 5], the high cost of medication strongly limits physician's access to these therapies for patients in the developing countries [6]. Therefore, extracts of the Chinese medicinal plant THH, which have shown easy access and anti-inflammatory activities in patients [7-12] and animal models [13, 14], have been widely used in China for centuries to treat immunological and inflammatory disorders. In the retrospective study, we demonstrate for the first time that THH is a promising and beneficial treatment to patients with active BD-associated uveitis, who were refractory to conventional immunosuppression.

Treatment with THH showed therapeutic efficacy in improving ocular and extraocular manifestations in patients with BD-associated uveitis. A significant potential of THH therapy in treating patients with active BD-associated uveitis seems to be its accomplishment in achieving 87.5% positive clinical response in patients within 2 years, showing 62.5% complete remission and 25% partial remission. Following THH therapy, disease score of ocular inflammation was significantly reduced ($p<0.0001$), and the incidence of ocular relapse decreased dramatically down to 0.4 ± 0.5 per year. Thus, the increasing and/or stabilization of visual acuity were detected in 75.8% patients receiving the therapy. FFA also confirmed the progressive resolution of retinal lesion caused by BD-associated uveitis. Cyclosporine A (CsA) and infliximab are generally used as the first line immunosuppressant in clinical practice for treatment of non-infectious uveitis, including BD-associated uveitis. In this retrospective study including 32 patients with active BD-associated uveitis, the efficacies of THH therapy, including clinical response rate, vision stabilization and/or improvement, long-term remission and relapse rate, are comparable to those received conventional immunotherapy as reported previously (Table 5) [4, 31-37]. Furthermore, THH therapy exhibited an overall significant improvement of extraocular manifestations in BD patients, particular genital ulcers and skin lesions as erythema nodosum and papulopustules ($p<0.0001$). A beneficial effect of THH in treating arthritis was also indicated in BD patients, and this effect is well correlated with the previous studies reported in humans and animal models [9, 14].

Table 4: Side effects of THH therapy in patients with BD-associated uveitis.

Adverse effect	No.	%	P value
ALT increasing	8	25	*0.005*
Total cholesterol increasing	5	15.6	0.053
Triglyceride increasing	8	25	*0.005*
Oligomenorrhea (female)	5	71.4	*0.021*
Amenorrhea (female)	2	28.6	0.462

*$p<0.05$ for significant difference between before and after THH therapy in patients, the Fisher's exact test. Glutamic-pyruvic transaminase (ALT); Oligomenorrhea and Amenorrhea occurred in 7 female patients only.

Table 5: Comparison of efficacy between THH and conventional immunotherapy.

				Efficacy			
Treatment	Eye (no)	Period (mon)	Clinical response (%)	BCVA Remission (%)	(%)	Relapse (%)	REF
THH	62	24-162	88	76	88	0.4	N/A
CsA	15-22	4-36	100	91-95	67	1.6	31,32
Infliximab	20-48	6-94	92	92-95	95-100	0-0.7	33-35
IFN-α	6-48	11-151	83-98	76-97	44-89	0.15	4,36,37

With regards to the safety profile, THH treatment showed fewer side effects in patients as compared to other Tripterygium preparations, in which severe adverse effects such as leukopenia, gastrointestinal symptoms and increased risk for infections were reported [38]. The main problem that we encountered with THH treatment was the side effect of irregular menstruation claimed in 71.4% female patients ($p<0.05$), which was dose-dependent and could be resolved rapidly while tapering down the dose of THH. This side effect of irregular menstruation caused by THH therapy is consistent with results from a human study for toxicity of THH preparations [39]. In spite of irregular menstruation seen in female patients, we also detected a transient increase of ALT and triglyceride in 25% patients receiving THH therapy ($p<0.01$), which disappeared shortly with no requirement for drug discontinuation.

No nephrotoxicity and blood cell counts abnormalities were observed in all patients during the period of observation (from 25 to 162 mon).

Not all patients with non-infectious uveitis (autoimmune uveitis) are responding for conventional immunotherapy, and severe systemic adverse effects occurred in some cases often lead to drug discontinuation and withdrawal of patients from therapies [3, 40]. THH therapy appears to be well tolerable to all patients. It is known that corticosteroids remain the cornerstone of treatment for inflammatory conditions, but their utility is limited by a plethora of side effects. Importantly, THH therapy was effective to achieve a long-term remission of BD-associated uveitis and corresponded with a minimized dose of corticosteroid, thus reach a key goal of immunotherapy across medical disciplines. Following treatment with THH, the maintenance dose of corticosteroids was utilized as low as 11.6 ± 5.45 mg daily, a half dose prior to THH therapy, and a statistical difference was detected before and after THH therapy ($p<0.01$). Most importantly, THH therapy is affordable and easy accessed compared to standard conventional immunotherapy. The daily expense for a maintenance dose is approximately 0.22-0.33 US dollars. This potential of THH therapy thus provide a great option for physicians to access for therapies worldwide.

In conclusion, our studies reveal that THH therapy has significant potential in treating patients with BD-associated uveitis, showing therapeutic promise on achievement of improvement of visual acuity and long-term remission. Comparing with conventional immunotherapy, THH therapy is well tolerable associated with minimized side effects. Specifically, THH therapy has an un-ignorable advantage of cutting off the expensive medical cost to achieve one of key goals of immunotherapy for patients' needs. Therefore, therapy with the Chinese medicinal plant THH may benefit BD patients unresponsive to conventional treatment.

6. Funding

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