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Complementary and alternative medicine in pediatric allergic disorders

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Abstract

Purpose of review—Allergic disorders represent serious public health problem in children. The chronic nature of these diseases and the fear of known side effects of synthetic drugs influence many families to seek complementary and alternative medicine (CAM). This review focuses on TCM herbal products, acupuncture for treating paediatric allergies.

Recent findings—Given the general safety profile, reputed efficacy, TCM are well received by the general population. However, compared to the long human use history and popularity of use of TCM, research into its efficacy and safety is still in infancy. Recent 2-3 years there are more controlled studies of TCM for allergic asthma, allergic rhinitis. Several publications including ours indicate that some TCM herbal formulas are safe and produced some levels of efficacy. Some herbal formula also showed beneficial immunomodulatory effects. Several preclinical studies demonstrated that the food allergy herbal formula-2 (FAHF-2) was effective in protecting against peanut anaphylaxis in animal model. Two TCM products have entered the clinical trials in the US for treating asthma and food allergy respectively. Both of these trials include children.

Summary—Recently studies indicate that TCM therapy including herbal medicines and acupuncture for allergic disorders in children is safe. There are also promising clinical and objective improvement. More controlled clinical studies are encouraged.

Keywords

Complementary and Alternative Medicine; traditional Chinese medicine; acupuncture; allergic disorders in children; Th1 and Th2 balance

Introduction

Over the past several decades, the number of individuals with atopic disease such as asthma, atopic dermatitis and food allergies has increased dramatically in industrialized countries. Among children up to 4 years of age, the incidence of asthma has increased 160%, and the incidence of atopic dermatitis has increased twofold to threefold[1]. Approximately 0.5-1% of the US population is affected by peanut allergy and the incidence has doubled in the past decade [2]. These figures demonstrate that allergic disorders in children are a serious public health problem, and the need to find new treatments for these disorders. Current conventional medications for allergic disorders for children are not fully satisfactory. There are also concerns of known side effects of corticosteroids [3;4] and long term use of β -2 agonists. The chronic and potentially life threatening nature of these diseases, and the lack of definitive preventive

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Footnote: U.S. Provisional Patent Applications regarding FAHF-2 (reference number 60554775) and ASHMI (PCT/US05/08600) have been filed.

and curative therapies lead many families to seek complementary and alternative medicine (CAM) treatments. Although the results of survey on CAM use by children varies between the studies, the reported rates by children with asthma ranges from 33% to 89% [5]. Because CAM therapies are generally considered to safe and effective by patients, and given the high rates of CAM use in children, health care providers need to educate themselves about these therapies, so they might better discuss the implications of using these therapies and potentially improve adherence to the prescribed medication regimen and improve allergy and asthma management [6]. A recent survey reported that pediatricians have a positive attitude towards CAM. A majority believe that their patients are using CAM, and that asking about CAM should be part of routine medical history. They would also consider referring to a CAM practitioner and want more education on CAM [7].

CAM is a group of diverse medical and health care systems, practices, and products that often are not integrated with conventional medicine. However, what is considered CAM in one country may be considered as part of standard treatment in another country or region [6]. For example traditional Chinese medicine (TCM) has long human use experience in China and other Asian countries such as Korea and Japan, and is part of main stream of medicine in these countries. In the US and other western countries, TCM is a major component of the CAM modality. TCM is a unique system of theory, diagnosis and treatments including herbal medicines, acupuncture and mind-body therapy. National Institutes of Health (NIH)/ National Center for Complementary and Alternative Medicine (NCCAM) defines TCM as Whole Medical Systems. [8] TCM therapies are mainly provided by the licensed practitioners and are beginning to play a role in US health care system. Acupuncture needles have been approved by the U.S. Food and Drug Administration (FDA) as medical device [9] and the cost of acupuncture is covered by some insurance policies. However, traditional Chinese herbal medicines are viewed as dietary supplements in the US and the cost not covered by most insurance policies. This may contribute to the gap between scientific evidence-based medicine and human use-based practice. The NCCAM/NIH now supports clinical and basic research on CAM. In recent years the US FDA has provided guidance for investigating botanical drug products, including complex formulas containing several herbs, focusing on efficacy, safety and consistency [10]. NIH support and FDA guidelines will foster the development of TCM derived botanical drugs in the US. Thus TCM products currently used as dietary supplements for asthma and allergy may be investigated as new botanical drugs. This communication focuses on controlled clinical trials of Chinese herbal medicines and acupuncture for asthma, allergic rhinitis, and food allergy based on the available publications including abstracts and review articles and updated research progress in the past 2 years.

A. Safety and efficacy of Chinese herbal therapy for childhood asthma

Asthma is a chronic inflammatory condition of the airways. It is believed that Th1 and Th2 responses are mutually antagonistic, such that they normally exist in equilibrium and cross-regulate each other. An optimum Th1-Th2 balance has been suggested as necessary to maintain healthy immune homeostasis. Loss of such balance has been hypothesized to underlie allergic asthma through a shift in immune responses from a Th1 (IFN- γ) pattern toward a Th2 (IL-4, IL-5, and IL-13) profile, which promote IgE production, eosinophilic inflammation, activation and survival, and enhanced airway smooth muscle contractility [11]. A recent study showed that low IFN- γ production in the first year of life was a predictor of wheeze during childhood [12]. Although corticosteroids (CS) improve asthma symptoms they do not alter the progression of asthma or cure the disease. [13] In addition to known side effects, CS withdrawal is often accompanied by increased inflammation in bronchial biopsies and symptomatic disease relapse. [14] This has been suggested to be due to CS induced overall suppression of both Th1 and Th2 responses. TCM formulas have been used for centuries to treat asthma, and there are a number of successful cases in children in the TCM literature [15]. Previous review by Bielory

and Lupoli provided some scientific evidence to support the use of TCM for asthma [16]. Recently, Li [17] reviewed 4 double blind placebo controlled studies of TCM herbal formulas for asthma. Among those, 3 studies Modified Mai Men Dong Tang (mMMDT) by Hsu et al [18], Ding Chuan Tang (DCT) by Chan et al [19] and STA-1 by Chang et al [20] involved only pediatric asthma (Table 1). One study of ASHMI by Wen et al [21] involved patients aged 18-60 years. Based on the definition of pediatric population by NIH as aged 21 and below, this study can be viewed as a study of older children and adults. There are also updated studies of ASHMI safety and tolerability and early efficacy in children and will also be described below.

1. ASHMI—Wen et al 2005 [21] reported the first double-blind, randomized, placebo-controlled trial investigating the efficacy and tolerability of an anti-asthma herbal medicine intervention. In this study (ASHMI, which contains 3 herbs, Table I) was compared to oral prednisone therapy in 91 patients 18-60 years of age with moderate-to-severe asthma. Subjects in the ASHMI group (45 patients) received oral ASHMI capsules (4 capsules, tid, 0.3 g/capsule) and placebo tablets similar in appearance to prednisone. Subjects in the prednisone group (46 patients) received oral prednisone tablets (20mg qd in the morning) and “ASHMI placebo capsules” for 4 weeks. Treatment was administered daily over 4 weeks. This study found that following treatment, lung function (FEV1 and peak expiratory flow values) was significantly improved in both ASHMI (64.9 ± 6.3 to 84.2 ± 6.5 ; $P < 0.001$) and prednisone (65.2 ± 6.3 to 88.4 ± 6.8 ; $P < 0.001$) groups. The improvement was slightly but significantly greater in the prednisone group. To understand the mechanisms underlying ASHMI's clinical effects immunological responses secondary to treatment were examined. Both ASHMI and prednisone decreased peripheral blood eosinophils, serum IgE, and Th2 cytokines (IL-5 and IL13) levels. Inhibition was greater in the prednisone group. However, unlike prednisone which suppressed IFN- γ secretion, ASHMI increased IFN- γ secretion [21]. Additional unique finding was that, in contrast to prednisone, which decreased serum cortisol, patients in the ASHMI treatment group levels were within the normal range. This result might be attributed to glycyrrhizin (a component of Gan-Cao), which affects the conversion of cortisol to cortisone, by inhibition of 11- β -hydroxysteroid dehydrogenase enzyme activity. [22]

We recently completed a study to examining the safety, tolerability and immunological effects of complementary ASHMI administration to standard therapy only in children 5-14 years of age with persistent asthma with or without allergic rhinitis in China. Subjects were randomly assigned to receive standard inhaled corticosteroid treatment (Budesonide - Pulmicort Turbohaler) plus ASHMI as complementary therapy (complementary ASHMI group, n=28) or inhaled corticosteroid treatment plus placebo (standard group, n=28). 51 patients completed the trial including 26 patients in the complementary ASHMI group and 25 in the standard group. The results showed that ASHMI was safe and well tolerated in children. As expected both standard and ASHMI + standard groups significantly improved FEV1, clinical symptoms. However, symptom scores improvement was greater in the ASHMI + standard group than in standard alone group, particularly in the nasal symptoms. Furthermore, ASHMI + standard group showed significantly greater reductions in serum total IgE ($p < 0.05$) and serum eosinophil cationic protein ($p < 0.05$) but higher serum IFN- γ levels ($p < 0.001$) after 3 months of treatment as compared to the standard therapy (Wen et al. manuscript in preparation).

2. Modified Mai Men Dong Tang (mMMDT)—Hsu et al [18] tested modified Mai Men Dong Tang (mMMDT, 5 herbs, table I) treatment of persistent, mild-to-moderate asthma in children. (Table I). This four-month trial included 100 asthmatics aged 5 to 18. The two active groups received 40 mg (40 patients), or 80 mg mMMDT (40 patients) for 2 months. The control group received placebo capsules (20 patients). Asthma medications were adjusted in a stepwise fashion equally in all three groups as follows: step 1, use of bronchodilator as needed; step 2, regular use of bronchodilator (theophylline or albuterol); step 3, regular use of two or three

drugs (theophylline, albuterol and cromolyn); step 4, addition of beclomethasone delivered with a metered-dose inhaler or alternate day methylprednisolone; and, step 5, addition of oral corticosteroids (> 0.5 mg/kg/day, with tapering). Any acute exacerbation of asthma was treated as directed by the child's physician using tapered doses of oral methylprednisolone. The investigators reported that relative to baseline, significantly greater increases in FEV1 were demonstrated in both mMMDT-treated groups in comparison with the placebo group ($P < 0.05$ for both doses of mMMDT), but no dose response effect was found between the two mMMDT treated groups. However, symptom scores were similarly improved in both mMMDT treatment groups. No drug-related adverse effects were reported. Blood tests, and liver and kidney function test results were within normal ranges during the study. This study did not find a significant reduction of IgE by DCT as compared to placebo

3. Ding Chuan Tang (DCT)—Chan et al[19] reported that in a randomized, double-blind clinical trial, Ding Chuan Tang (DCT), a nine herb formula (Table I), reduced airway hyper-reactivity (AHR) in stabilized asthmatic children. This study enrolled children between 8 and 15 years of age diagnosed with mild-to-moderate persistent asthma. Patients were randomly allocated to receive 6.0 g DCT or placebo daily for 12 weeks. Fifty-two asthmatic children completed the study. Both groups received standard asthma management in a stepwise fashion (5 steps) as outlined above in the Hsu study (11). Twenty-eight patients were assigned to the treatment group and 24 to the placebo group. At the end of the treatment period, AHR determined by log PC(20) was significantly improved in the DCT group (0.51 ± 1.05 mg/ml vs. 0.26 ± 0.84 mg/ml, $p = 0.034$). Clinical and medication scores showed improvement in the DCT group ($p = 0.004$). The authors concluded that more stable airways were achieved by this add-on complementary therapy. This study did not find a significant reduction of IgE by DCT as compared to placebo.

4. STA-1—Chang et al[20] reported results of a clinical evaluation of STA-1 and STA-2 herbal formulas [Table 1]. STA-1 and STA2-2 are combinations of mMMDT (10 herbs) and Lui-Wei-Di-Huang Wan (LWDHW, 6 herbs). STA-1 and STA-2 reportedly differ only in the preparation procedures of LWDHW. The six herbs in LWDHW were milled to a powder for STA-1, and extracted in boiling water for STA-2. Overall, 120 patients, 5 to 20 years of age with mild-to-moderate asthma were included in this study. Forty four patients were treated with STA-1 at a dose of 80 g/kg/day and forty were treated with STA-2 at a dose of 80 g/kg/day, and 16 patients received a placebo. Treatment was administered twice daily for 6 months. All patients were provided with asthma medications adjusted in a stepwise fashion as described above in the Hsu et al. mMMDT study.(11) Completion rates were 88%, 80% and 80% for STA1, STA2 and placebo respectively. The results showed a statistically significant reduction of symptom scores, systemic steroid dose, and total IgE and specific IgE levels in the STA-1 group. Furthermore, STA-1 improved pulmonary lung function FEV(1) as compared with the placebo group. STA-2 treated patients showed no significant improvement in any parameter. The authors speculated that some as yet unknown heat-sensitive compounds in LWDHW possess anti-inflammatory activity. This study also found that total and specific IgE levels were significantly reduced by herbal therapy (STA-1) as compared to placebo treatment.

In summary, the above studies demonstrated consistent safety of herbal formulas for asthma used in children and some degree of positive clinical improvement. It should be pointed out that since standard therapy is sufficient to improve symptoms and lung function, TCM clinical efficacy as complementary therapy might have been masked by the corticosteroid effect during the short period of treatment and observation. Given the safety profile, long term treatment should be considered. ASHMI has received US FDA IND approval (IND 71 526) for phase I and II clinical trials for treating asthma. A phase I study has been completed. Based on clinical and laboratory test results, ASHMI was considered safe and well tolerated.[23] A phase II study, involving 60 patients over 6-months duration is underway.

B. Safety and efficacy of acupuncture for asthma and allergic rhinitis in children

Acupuncture therapy is well accepted by the general population, including children. The U.S. Food and Drug Administration (FDA) approved acupuncture needles as medical device and regulates their use by licensed practitioners. Recently, Jindal et al [24] reviewed 31 published journal articles, including 23 randomized controlled clinical trials and 8 meta-analysis/systematic reviews addressing safety and efficacy of acupuncture in children. A very low risk was associated with acupuncture in pediatrics. Acupuncture seems to be most effective in preventing postoperative induced nausea, pain relief [25]. Controlled studies of acupuncture for asthma and allergy in children are limited; only 2 publications are available in the past 5 years (Table I). In the study by Stockert et al [26], 17 children aged 6-12 yr with intermittent or mild persistent asthma were enrolled in a randomized, placebo-controlled, double-blind pilot study. Eight patients received laser acupuncture for 10 wk and probiotic treatment in the form of oral drops for 7 wk. Nine patients in the control group were treated with a laser pen which did not emit laser light and were given placebo drops. Patients in the TCM group had fewer days of acute febrile infections when compared with the control group [1.14 (1.4) vs. 2.66 (2.5), $p = 0.18$]. There was no difference in lung function between the groups. In a study of acupuncture for allergic rhinitis by Ng et al²⁷, 72 children over the age of 6 years were randomized to receive either acupuncture or sham acupuncture for 8 weeks. During the 12-week follow-up period, the acupuncture group reported significantly better daily rhinitis scores (5.43 vs. 7.19 in the sham group, $P = 0.03$) and symptom free days (12.7 vs. 2.4 in the sham group, $P = 0.0001$). However, no significant differences were found in relief medication use, nasal or blood eosinophil counts, or serum immunoglobulin E levels. Because of the popularity of acupuncture and some preliminary reported positive clinical results, controlled studies of acupuncture on asthma and allergy should be encouraged. However, given the nature of acupuncture practice, it might be difficult to apply double blind and placebo (sham needles) controlled clinical study. There is a need to develop suitable methodology.

C. Development of herbal interventions for food allergy

While tremendous strides have been made in food allergy awareness, there is no satisfactory therapy to prevent or reverse the disease. PNA imparts a significant psychological burden on the allergic individuals and their families [27]. An effective treatment would offer a life-altering option for those affected. Studies of TCMs for food allergy are rare. Our group for the first time developed food allergy herbal formula 1 (FAHF-1) and then refined formula FAHF-2 by eliminating 2 herbs from the FAHF-1. The following section summarizes both preclinical and preliminary clinical results of FAHF-2 studies.

Preclinical studies of efficacy and safety of FAHF-2 on peanut and multiple food allergies—FAHF-2, containing 9 herb extracts derived extracts of 11 herbs. [28;29] Using a well established murine model peanut allergy, we found that FAHF-2 completely blocked peanut induced anaphylaxis when administered intragastrically (i.g.) during the development of peanut hypersensitivity [29], or when administered after peanut hypersensitivity was fully established [30] Recently, we showed that FAHF-2 provides persistent protection for almost a quarter of the mouse life-span after a single course of treatment, and also maintained the long term beneficial immunomodulatory effect. [31] It has been shown that multiple food allergies are more common than single food allergy. [32] We recently developed a multiple food allergy model (peanut, egg and fish allergies and test the effect FAHF-2 in this model. We showed that FAHF-2 provided complete protection from anaphylaxis to oral challenge with every allergen [33].

The mechanisms underlying FAHF-2 protection against food induced anaphylaxis are at multiple levels. We showed FAHF-2 suppressed histamine release, reduced serum IgE but increased IgG2a. [30] The protective effect was associated with up-regulation of Th1 and down-

regulation of Th2 cytokines. Thus, FAHF-2 exhibits an immunomodulatory effect, but not overall immunosuppressive effects. A similar immunomodulatory effect on peripheral blood mononuclear cells from children (aged 3-12 years) with peanut allergies has also been found in a study, in which FAHF-2 significantly reduced peanut stimulated IL-5 production and increased IFN- γ production [34]. We also found that FAHF-2 inhibited Fc ϵ RI expression on mast cell and basophils in vivo, and inhibited mast cell degranulation in vitro [35].

3. Clinical investigation of safety of FAHF-2 for food allergy

Given the excellent efficacy and safety profile in animal studies, FAHF-2 is an ideal candidate to develop a treatment for human food allergy. We have received IND approval from the US FDA, and then IRB approval, and began a FAHF-2 clinical study in 2008. This is the first clinical investigation of a botanical drug for multiple persistent food allergy including peanut, and/or tree nut, fish and shellfish allergies, and the first botanical drug trial that includes children. We now have completed a double blind, dose escalation phase I study on 18 patients (12 patients in FAHF-2 and 6 in placebo) with peanut and other food allergies. The results showed that FAHF-2 is safe and well tolerated (Wang et al manuscript is in preparation) An extended 6 month phase I open label study is currently underway. After completion of this study, we will conduct a double blind, placebo controlled phase II study involving 120 patients.

Conclusion

Investigation of TCM herbal therapy for children for asthma is an active area of research. Several recent studies reported that these TCM formulas are safe and had a positive effect on symptoms and/or lung function in children when used as monotherapy or complementary therapy. ASHMI also showed enhancement of IFN- γ and serum cortisol levels, of potential benefit for asthma therapy. These results demonstrated that TCM herbal formulas have potential as CAM therapy for asthma treatment. Currently a phase II study of ASHMI is ongoing in the US to investigate whether ASHMI can reduce or replace corticosteroid use and assess long term safety. FAHF-2 showed excellent long term protection and beneficial immunomodulation effect in mice. ASHMI and FAHF-2 may prove to be the first generation of anti asthma and food allergy botanical drugs.

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Abbreviation (alphabetic order)

AHR	airway hyperresponsiveness
ASHMI	Anti-asthma herbal medicine intervention
CAM	complementary and alternative medicine
CS	corticosteroids
DCT	Ding Chuan Tang, classical formula

DP	Dermatophagoides pteronyssinus
FAHF-1	Food allergy herbal formula-1
FAHF-2	Food allergy herbal formula-2
LWDHW	Lui-Wei-Di-Huang Wan, classical formula
mMMDT	Modified Mai Men Dong Tang, modified classical formula
MSSM-002	Herbal formula
NCCAM	National Center for Complementary and Alternative Medicine
PN	peanut
PNA	peanut allergy
TCM	traditional Chinese medicine
Wk wks	weeks

Table 1

Chinese herbal medicines and acupuncture for paediatric asthma and allergic rhinitis

Herbal remedies			Acupuncture		
	ASHMI[21] (2005)	mMMDT[18] (2006)	Ding Chuan [36] (2006)	STA-1[20] (2006)	NA [26] 2007
Publication Date					2004
Number of Herbs	3	5	9	10	NA
Type of study	RCT	RCT	RCT	RCT	RCT
Sample size	n = 45 ASHMI n = 46 Prednisone	n = 40 mMMDT 80mg n = 40 mMMDT 40mg n = 20 Placebo	n = 28 DCT n = 24 Placebo	n = 50 STA-1 n = 50 STA-2 n = 20 Placebo	n=33 AA n = 32 SA
Ages (years)	18-65	5-18	8-15	8-15	6-21
Indication	Moderate-to-severe persistent asthma	Mild-to-moderate persistent asthma	Mild-to-moderate persistent asthma	Mild-to-moderate persistent asthma	Intermittent or mild persistent asthma
Length of Study	4 weeks	4 months	3 months	6 months	10 wks
Herbal Components [37;38] Or acupuncture points	1 Radix Glycyrrhizae 2 Radix Sophorae Flavescentis 3 Ganoderma	1 Radix Glycyrrhizae 2 Radix Ophiopogonis 3 Radix Panacis Quinquefolii 4 Tuber Pinellia 5 Herba Tridacis procumbentis	1 Radix Glycyrrhizae 2 Tuber Pinellia 3 Ginkgo Bilboae 4 Herba Ephedrae 5 Flos Tussilaginis Farfarae 6 Cortex Mori Albae Radicis 7 Fructus Perilla Frutescens 8 Semen Pruni Armeniacaee 9 Radix Scutellariae Baicalensis	Combined formula of mMMDT without the herb #5 with Lui Wei Di Huang Wan (6 hrbs)	Up to 16 points, individualized treatment
Improved FEV1	yes	yes	yes	yes	No
Improved Symptom score	yes	yes	yes	yes	No, but fewer days of acute febrile infections fewer
					Yes (Significantly lower daily rhinitis scores and more symptom-free days than SA)

All the herbals are Chinese original. All formulas contain Radix Glycyrrhizae. RCT: Randomized, placebo-controlled, double-blind, clinical trial; This table is a modification of the table in Li, J Allergy. Clin Immunol[17] with permission.. RLA: real laser acupuncture; RA: real acupuncture; SA: Sham acupuncture.