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Treatment of food anaphylaxis with traditional Chinese herbal remedies – from mouse model to human clinical trials

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Abstract

Purpose of review—To describe the development of a novel treatment for food allergy, named the food allergy herbal formula-2 (FAHF-2), that is based on Traditional Chinese Medicine.

Recent findings—FAHF-2 has proven to be safe and effective for the treatment of food allergies in murine models of peanut and multiple food allergies. These results are accompanied by evidence of favorable immune modulation, and the effects are persistent after discontinuation of treatment. Early clinical trials demonstrate the safety and tolerability of this formula in subjects with food allergies. An on-going Phase II clinical trial will evaluate the efficacy of FAHF-2 in protecting individuals from allergen-induced allergic reactions during oral food challenges.

Summary—FAHF-2 is an herbal formula that has a high safety profile and has shown to prevent anaphylaxis in murine models of food allergy. Similar findings in clinical trials could bring a novel treatment for food allergies.

Keywords

food allergy; anaphylaxis; treatment; Traditional Chinese Medicine; herbs

Introduction

Food allergy continues to be a public health concern, now affecting up to 8% of children and 3% of adults.[1,2] The 8 food allergens accounting for the majority of reactions are: milk, egg, wheat, soy, peanut, tree nuts, fish and shellfish.[3] While some allergies such as milk and egg are often transient, allergies to peanut, tree nuts, fish and shellfish are often life-long. The current standard of care is the avoidance of food allergens and preparedness for potentially life-threatening allergic reactions. While there are obvious medical concerns related to food allergy management, the impact of food allergies reaches beyond the affected individual, extending into social, public health (schools, restaurants, etc) and economic realms as well. Thus, there are many compelling reasons to develop effective treatments or cures for food allergy.

In recent years, there has been growing interest in using complementary or alternative approaches in the management of various medical disorders. 2007 NHIS study reported that 38% of adults and 12% of children had used complementary or alternative medicine (CAM) in the past year, with the annual expenditure for CAM exceeding \$30 billion.[4] In fact, Eisenberg found that many people spend far more money on CAM-related techniques or supplies than they are willing to spend on physician visits or western medications.[5]

Traditional Chinese medicine (TCM) has been used in China and other Asian countries for thousands of years, either as monotherapy or in combination with standard Western medical treatment, to manage the entire spectrum of medical disorders. One component of TCM is herbal therapy, and the main principal underlying the use of herbal formulas is that complex interactions between herbs produce synergistic effects that can reduce possible side effects of individual herbs. While food allergy has not been a prominent issue in Eastern countries and therefore, is not a disorder that can be searched for in TCM texts, parasitic illnesses with symptoms similar to those seen in food-induced anaphylaxis can be found in the TCM literature.[6] Thus, the strong desire to develop treatments for food allergy combined with growing interest in using novel or alternative approaches to treatment led to the exploration of TCM as a possible novel therapy for food allergies.

Wu-Mei Wan is a 10-herb classical formula used for the treatment of intestinal parasite infections.[6] It was first documented in a classical Chinese medical textbook compiled some 2000 years ago. The indication for use of this has many similarities to the symptoms of anaphylaxis. Wu-Mei Wan has also been demonstrated to be effective for gastroenteritis and asthma in Chinese clinical studies.[7] In the development of a formula for food allergy, an additional herb was included, Ling Zhi, which has shown to have anti-allergy and anti-inflammatory properties.[8,9] This 11-herb formula was named the food allergy herbal formula 1 (FAHF-1).[10] Subsequently, 2 herbs (Xi-Xin and Zhi-Fu-Zi) were removed from the formula to improve the safety profile as these 2 herbs are potentially toxic if processed improperly. The resulting 9-herb formula, named the food allergy herbal formula 2 (FAHF-2), is used for the murine and clinical studies.[11]

The components of FAHF-2 are shown in Table 1. Ling Zhi and Wu Mei comprise the largest part of FAHF-2.

FAHF-2 effects in murine models of food-induced anaphylaxis

The high safety profile of FAHF-2 was demonstrated in an experiment where mice were fed 24 times the effective daily dose.[11] These mice exhibited no signs of acute toxicity, and all appeared healthy 2 weeks after the dose. Results for complete blood counts and biochemical assays for renal and hepatic function were within the normal range, and no abnormalities were seen on histology of the major organs (kidney, liver, heart, spleen, lung, stomach, and intestines).

The efficacy of FAHF-2 was tested using a murine model of peanut anaphylaxis. C3H/HeJ mice were sensitized with peanut and cholera toxin as previously described.[11] FAHF-2 treatment was administered orally twice a day for 7 weeks. This dose was based on a version of the equivalent effective daily dose from humans to the mouse based on body surface area.

Post-treatment challenges showed that FAHF-2 treated mice were protected from peanut-induced anaphylaxis, with symptom scores, body temperatures and plasma histamine levels demonstrating lack of allergic reaction, similar to naïve mice. In contrast, sham treated mice had severe, near-fatal reactions, significant drops in body temperature, and elevated plasma histamine levels with each of the peanut challenges. The FAHF-2 treated group was protected from anaphylaxis for nearly 6 months, and the effect was present both when FAHF-2 was administered early in the peanut sensitization process and when treatment was given after peanut allergy had been established.[12,13] Treatment effect appeared to wane after approximately 6 months; however, a second course of treatment with FAHF-2 re-established the protection from peanut-induced anaphylaxis.

In addition to the clinical parameters, significantly decreased peanut-specific IgE was seen in the FAHF-2 treated mice by the fourth week of treatment (week 12). Peanut-specific IgE remained lower in the FAHF-2 treated group even after discontinuation of treatment; this effect paralleled the clinical effects and was evident through week 50 (Figure 1). Peanut-specific IgG2a levels were conversely significantly elevated by the fourth week of treatment and continued to be elevated through week 50.

In addition, sustained modulation of cytokines was seen at week 50 with significant reductions in production of the Th2 cytokines, IL-4, IL-5, and IL-13, by cells of the mesenteric lymph node and splenocytes. Enhanced production of interferon-gamma was seen, demonstrating that skewing of the immune system rather than immunosuppression is at play. Interferon-gamma has been shown to contribute to the down-regulation of Th2 cytokines and reduction of IgE production, and thus appears to be one of the mechanisms by which FAHF-2 mediates protection from peanut-induced anaphylaxis in the murine model of peanut allergy.[14, 15]

To further elucidate the potential mechanisms of action of FAHF-2, effects on mast cell and basophils were investigated.[16] A reduction in peripheral blood basophils and peritoneal mast cells was seen, as well as a decrease in mast cell FcεRI expression, however, basophil FcεRI expression was unaffected. In vitro effects of FAHF-2 on a murine mast cell line (MC/9 cells) showed inhibition of IgE-mediated proliferation and degranulation (using anti-DNP IgE). These findings indicate that FAHF-2 directly suppresses basophil and mast cell activities.

Using a murine model of multiple food allergies (to peanut, egg and fish), FAHF-2 proves to be food allergen non-specific, suggesting potential clinical applications for all food allergic individuals. Similar to earlier experiments, the same dose of FAHF-2 was administered twice a day for 7 days after the mice had been sensitized and boosted to all 3 allergens.[17] Post-treatment challenges for peanut, egg and codfish showed protection from anaphylaxis as evidenced by lack of symptoms, lack of change in body temperature, no change in plasma histamine level after each of the food challenges. Reduction in allergen-specific IgE and increased specific IgG2a levels were seen, along with significant decreases in Th2 cytokine production and increased IFN-gamma production by splenocytes and mesenteric lymph node cells.

Clinical Trials

Based on the promising results from the murine models demonstrating effective and durable protection from anaphylaxis and favorable immunomodulation, FDA approval of FAHF-2 as an investigational new drug was obtained in 2007 (IND 77,468). The first steps in clinical development of this formula were standardization of the raw herbs, manufacturing process, and final product. All herbs originate from China and are inspected by licensed pharmacists to ensure the identity and quality of the herbs.[18] Extensive safety data testing is performed, including limit testing of pesticides, heavy metals and microbials. Although the traditional method for administering herbal medicines is in the form of decoctions to be taken orally, FAHF-2 is produced in tablet form, which is more acceptable to Western palates and more conducive for use in clinical trials. Consistency of the final product is assessed with HPLC fingerprinting.

The first clinical trial was a double-blind, placebo-controlled dose escalation trial (acute Phase I trial).[18] Subjects between 12-45 years of age who had documented peanut, tree nut, fish, and/or shellfish allergy (based on history and positive skin test and/or detectable food-specific IgE) were enrolled. Subjects took 4, 6, or 12 tablets three times a day for 7 days. FAHF-2 was well-tolerated, with no significant adverse effects seen (clinical report, laboratory parameters measuring complete blood count and complete metabolic profile, urinalysis, electrocardiogram and pulmonary function tests). Although not a primary endpoint of the study, laboratory studies were performed to assess for early indications of immunologic effect. Ex vivo effects of FAHF-2 on cytokine levels in peripheral blood mononuclear cells from subjects pre and post-FAHF-2 treatment showed significant decrease in IL-5 production by PBMCs from the treated group that was not seen in the placebo group. No other immunologic changes were seen after this short course of treatment.

Since TCM herbal formulas are generally prescribed for chronic use, the long-term safety and tolerability of FAHF-2 was assessed in an extended phase I trial.[19] In this open-label study, subjects received 6 tablets of FAHF-2 three times a day for 6 months. 18 subjects were enrolled, and 14 subjects completed treatment. Four subjects withdrew from the trial: 2 subjects had difficulties with time commitment and adherence, 1 with transient abdominal complaints without vomiting or diarrhea, and 1 due to pregnancy. Results of this study demonstrated that prolonged treatment with FAHF-2 was well-tolerated, with no significant adverse effects. Some evidence of favorable immunomodulatory effects were also seen in this small sample of patients. Suppression of allergen-stimulated basophil activation (CD63 expression) was seen after 6 months. There was also a trend toward reduction in peripheral blood basophil and eosinophil percentages after 6 months of FAHF-2 treatment.

Currently, a phase II clinical trial is on-going to assess the efficacy for FAHF-2 for the treatment of food allergies. 68 subjects, ages 12-45 years, with peanut, tree nut, sesame, fish or shellfish allergy have been enrolled at 3 sites in this randomized double-blind, placebo controlled study. Subjects are randomized to receive 10 tablets of FAHF-2 or placebo three times a day for 6 months (2:1, FAHF-2:placebo). The primary outcome is the change in threshold dose of allergen to induce a reaction during a double-blind, placebo-controlled oral food challenge. Secondary outcomes include changes in prick skin test sizes, allergen

specific IgE and IgG4 levels, epitope recognition using peptide microarray immunoassay, basophil activation and T cell activity.

Future directions

The daily dose of FAHF-2 is large, making it a difficult treatment regimen to adhere to for long periods of time. Several strategies for reducing this daily dose have been explored, including reducing the number of components in the formula, alternate methods of extraction, and identification and isolation of active compounds.

In a series of experiments using the murine model of peanut allergy, the relative effectiveness of each individual herb was examined for both clinical and laboratory parameters.[20] No individual herb was as effective as the FAHF-2 formula at protecting the mice from peanut-induced anaphylaxis, suppressing peanut specific IgE and increasing peanut specific IgG2a. While a few herbs did provide protection in some mice for some parameters, the effect was not consistent across all parameters measured. For example, while Huang-Bai showed some efficacy at protecting some mice from the symptoms of anaphylaxis, treatment with this herb did not result in any changes in peanut-specific IgE or IgG2a. A simplified formula of 3 herbs (Huang-Bai, Ling Zhi and Gan-Jiang) that were most effective in reducing the symptoms of anaphylaxis and/or Th2 cytokine production also did not achieve the same level of effectiveness as the FAHF-2 formula. These results indicate that the efficacy of FAHF-2 probably rests on the synergy of all 9 herbs, which are necessary to provide complete and durable protection against anaphylaxis and the associated immunomodulatory effects.

A refined FAHF-2 has been developed using an additional butanol purification step (B-FAHF-2).[21] In the murine model, B-FAHF-2 at 1/5 the dose of FAHF-2 confers a similar level of protection from peanut-induced anaphylaxis. Similar to the original formula, B-FAHF-2 treated mice have no symptoms of allergy upon challenge with peanut, are able to maintain their body temperatures and lack elevations in plasma histamine levels. These effects are durable, lasting up to 6 months. Immunologic effects are also consistent with the original formula. There is suppression of peanut-specific IgE and enhancement of peanut-specific IgG2a. Th2 cytokine production (IL-4, IL-5 and IL-13) by splenocytes and mesenteric lymph nodes are decreased, but interferon-gamma production is increased in treated mice. Consistent with the original formula, re-treatment with a second course of B-FAHF-2 re-establishes protection after treatment effects wane. Furthermore, the safety profile of B-FAHF-2 is similar to FAHF-2.

On-going efforts to identify active compounds have focused on fractionating FAHF-2 based on polarity using prep-HPLC. The effects of these fractions were first tested on the RBL-2H3 cell line as an in vitro model, using the β -hexosaminidase assay to assess impact on mast cell degranulation. The fraction that contained primarily alkaloid compounds (fraction 2) significantly reduced β -hexosaminidase release.[16] Similar results were seen for the alkaloid fraction using human skin mast cells. Using liquid chromatography mass spectrometry, the three major alkaloid components of this fraction were identified to be berberine, palmatine, and jatrorrhizine. These individual compounds inhibited mast cell degranulation in RBL-2H3 cells in a non-toxic, dose-dependent manner and the combined

effects significantly inhibited Syk phosphorylation, but none of these compounds inhibited IgE binding to mast cells. Additional studies using cultured macrophages (RAW264.7) and human B-cells (U266 human myeloma cells) demonstrated that the same 3 alkaloids (berberine, palmatine, and jatrorrhizine) showed strong inhibition of B cell IgE production. [22] Further studies to identify the key players within FAHF-2 will lead to a better understanding of the mechanism of action of the formula, and hopefully lead to refined dosing strategies.

Conclusions

Results from both murine experiments and early clinical trials suggest that FAHF-2 may be an effective approach to food allergy treatment that is not specific to any one food allergen, and can be potentially used to treat multiple food allergies. The on-going Phase II clinical trial should yield much anticipated information regarding effects of this formula on human food allergies.

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References

1. Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics*. 2011; 128:e9–17. [PubMed: 21690110]
2. Liu AH, Jaramillo R, Sicherer SH, et al. National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005–2006. *J Allergy Clin Immunol* 2010. 126:798–806. e13.
3. Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the Diagnosis and Management of Food Allergy in the United States: Summary of the NIAID-Sponsored Expert Panel Report. *J Allergy Clin Immunol*. 2010; 126:1105–18. [PubMed: 21134568]
4. Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007. *Natl Health Stat Report*. 2008; 12:1–23. [PubMed: 19361005]
5. Eisenberg DM, Kessler RC, Foster C, et al. Unconventional medicine in the United States. Prevalence, costs, and patterns of use. *N Engl J Med*. 1993; 328:246–52. [PubMed: 8418405]
6. Bensky D. Gamble A: Chinese Herbal Medicine. In *Materia Medica*. Revised ed. Seattle: Eastland Press. 1993
7. He FH, Wu WP. Clinical application of Wu-Mei-Wan. *Zhong Gui Yi Yao Xue Ba*. 2004; 19:748–50.
8. Huang, KC. The pharmacology of Chinese herbs. 2nd ed.. CRC Press; Boca Raton (FL): 1999. p. 118-20.
9. Tasaka K, Akagi M, Miyoshi K, et al. Anti-allergic constituents in the culture medium of *Ganoderma lucidum*. (I). Inhibitory effect of oleic acid on histamine release. *Agents Actions*. 1988; 23:153–6. [PubMed: 2455975]
10. Li XM, Zhang TF, Huang CK, et al. Food Allergy Herbal Formula-1 (FAHF-1) blocks peanut-induced anaphylaxis in a murine model. *J Allergy Clin Immunol*. 2001; 108:639–46. [PubMed: 11590394]
11. Srivastava KD, Kattan JD, Zou ZM, et al. The Chinese herbal medicine formula FAHF-2 completely blocks anaphylactic reactions in a murine model of peanut allergy. *J Allergy Clin Immunol*. 2005; 115:171–8. [PubMed: 15637565]

12. Qu C, Srivastava K, Ko J, et al. Induction of tolerance after establishment of peanut allergy by the food allergy herbal formula-2 is associated with up-regulation of interferon-gamma. *Clin Exp Allergy*. 37:846–55. 200. [PubMed: 17517098]
13. Srivastava KD, Qu C, Zhang T, et al. Food Allergy Herbal Formula-2 silences peanut-induced anaphylaxis for a prolonged posttreatment period via IFN-gamma-producing CD8+ T cells. *J Allergy Clin Immunol*. 2009; 123:443–51. [PubMed: 19203662]
14. Pene J, Guglielmi L, Gauchat JF, et al. IFN-gamma-mediated inhibition of human IgE synthesis by IL-21 is associated with a polymorphism in the IL-21R gene. *J Immuno*. 2006; 177:5006–13.
15. Lewkowich IP, Hayglass KT. Endogenous IFN-gamma and IL-18 production directly limit induction of type 2 immunity in vivo. *Eur J Immunol*. 2002; 32:3536–45. [PubMed: 12442336]
16. Song Y, Qu C, Srivastava K, et al. Food allergy herbal formula 2 protection against peanut anaphylactic reaction is via inhibition of mast cells and basophils. *J Allergy Clin Immunol*. 2010; 126:1208–17. e3. [PubMed: 21134573]
- 17**. Srivastava KD, Bardina L, Sampson HA, et al. Efficacy and immunological actions of FAHF-2 in a murine model of multiple food allergies. *Ann Allergy Asthma Immunol*. 2012; 108:351–358. e1. [PubMed: 22541407] [This study demonstrates that FAHF-2 treatment is not allergen-specific, thus, may have applications for a range of food allergies.]
18. Wang J, Patil SP, Yang N, et al. Safety, tolerability, and immunologic effects of a food allergy herbal formula in food allergic individuals: a randomized, double-blinded, placebo-controlled, dose escalation, phase 1 study. *Ann Allergy Asthma Immunol*. 2010; 105:75–84. [PubMed: 20642207]
19. Patil SP, Wang J, Song Y, et al. Clinical safety of Food Allergy Herbal Formula-2 (FAHF-2) and inhibitory effect on basophils from patients with food allergy: Extended phase I study. *J Allergy Clin Immunol*. 2011; 128:1259–1265. e2. [PubMed: 21794906]
20. Kattan JD, Srivastava KD, Zou ZM, et al. Pharmacological and immunological effects of individual herbs in the Food Allergy Herbal Formula-2 (FAHF-2) on peanut allergy. *Phytother Res*. 2008; 22:651–9. [PubMed: 18389474]
21. Srivastava K, Yang N, Chen Y, et al. Efficacy, safety and immunological actions of butanol-extracted Food Allergy Herbal Formula-2 on peanut anaphylaxis. *Clin Exp Allergy*. 2011; 41:582–91. [PubMed: 21121976]
22. Yang N, Song Y, Sampson H, Li XM. Bioactivities of berberine, palmatine, and jatrorrhizine isolated from food allergy herbal formula 2 (FAHF-2). *J Allergy Clin Immunol*. 2011; 127:AB240.

Key bullet points

1. FAHF-2 treatment in peanut allergic mice results in protection from peanut-induced anaphylaxis that persists for approximately 6 months.
2. In the murine model, protection from anaphylaxis is associated with decreased allergen-specific IgE, increased IgG2a, decreased Th2 cytokines production and, increased IFN-gamma production.
3. Given the high safety profile and effectiveness in the murine model, clinical trials in humans are underway. Phase I clinical trials demonstrated safety of FAHF-2 in food allergic individuals, and a Phase II study investigating efficacy is on-going.
4. Studies are on-going to identify active compounds and elucidate the mechanisms of action of this herbal formula.

Figure 1. FAHF-2 treatment produced persistent reduction in peanut-specific IgE levels and increased IgG_{2a} levels

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FAHF-2 treatment produced prolonged reduction in serum peanut (PN)-specific IgE and increased IgG_{2a} levels. Sera were harvested after blood collection by retro-orbital bleeding at indicated time points. Serum peanut-specific IgE levels (A) and specific IgG_{2a} levels (B) were determined by ELISA. Data points indicate group means $\pm$ SEMs (n=8)

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ vs sham. The scale of the x-axis is not linear.

TABLE 1Components of herbal medicines in FAHF-2^{*}

Name of TCM Materia Medica (Pin Yin)	Equivalent pharmaceutical name	Part used	Amount (% or total)
Ling Zhi (Chi)	Ganoderma Lucidum	Fruiting body	28.17
Wu Mei	Fructus Pruni Mume	Fruit	28.17
Chuan Jiao	Pericarpium Zanthoxyli Bungeani	Seed	1.41
Huang Lian (Chuan)	Rhizoma Coptidis	Root	8.46
Huang Bai	Cortex Phellodendri	Root	5.63
Gan Jiang	Rhizoma Zingiberis Officinalis	Root	8.45
Gui Zhi	Ramulus Cinnamomi Cassiae	Twig	2.81
Ren Shen (Hong)	Radix Ginseng	Root	8.45
Dang Gui (Shen)	Corpus Radix Angelicae Sinensis	Root	8.45

TCM, Traditional Chinese Medicine

^{*} All of the herbs are of Chinese origin.