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Double-Blind Placebo Controlled Trial of Dapsone in Antihistamine Refractory Chronic Idiopathic Urticaria

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Abstract

Background—Management of antihistamine refractory CIU has poorly defined therapeutic options.

Objective—To evaluate the efficacy of dapsone in antihistamine refractory CIU compared to placebo.

Methods—Twenty-two patients with antihistamine refractory CIU were randomly assigned to 100 mg of dapsone daily or placebo for 6 weeks in a 14 week double-blind, placebo-controlled crossover trial. Endpoints were measured from a daily diary reflecting weekly hive score (WHS) and weekly itch score (WIS) and a visual analog score. Secondary to a carryover effect, the first period results were analyzed as a parallel design comparing placebo to dapsone directly using repeated measures analysis.

Results—After 6 weeks patients in the dapsone arm showed mean improvement over baseline in VAS (+2.3 [0.6,4.1], $p=0.01$), urticaria score (-3.5 [-6.2, -0.9], $p=0.01$), and itch score (-4.8 [-7.6, -2.1], $p=0.001$), whereas the placebo arm showed no improvement over baseline for VAS, urticaria or itch scores. Dapsone showed greater improvement compared to placebo for itch ($p=0.047$) and VAS ($p=0.04$). Of the 22 patients, 3 showed complete resolution of hives and itch

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with dapsone, while 31% and 41% had 50% resolution of hives and itch respectively. No serious adverse effects were observed from dapsone.

Conclusion—To our knowledge, this is the first DBPC study of dapsone in CIU and suggests dapsone has efficacy in antihistamine refractory CIU patients.

Keywords

Dapsone; chronic idiopathic urticaria; Urticaria; RCT; antihistamine

Introduction

Chronic idiopathic urticaria (CIU) is defined as persistent urticaria greater than 6 weeks in duration and without an identifiable cause (1). Symptoms of CIU include relentless pruritus, cosmetically disfiguring wheals, sleep disturbance, altered emotions, and difficulties with daily activities, all of which can be debilitating and impact disease-related quality of life (QOL) with health status scores comparable to patients with coronary artery disease (2, 3). The disease has been estimated to being as high as 0.5-1% of the population and up to 20% of sufferers may continue to have symptoms 20 years after onset (4, 5).

First line treatment for CIU is a nonsedating H₁ antihistamine, to which nonresponders often require 4 times the FDA approved dosage (6). Unfortunately, many patients fail to achieve satisfactory control with an antihistamine alone and to date no alternative therapy has been fully accepted or received regulatory approval (6, 7). Acutely, corticosteroids are the most widely used therapy for antihistamine refractory CIU; however, due to toxicity this therapy is usually reserved for short-term use in refractory or severe disease (7, 8). Other alternative agents for CIU have been investigated, notably leukotriene modifiers, cyclosporine and more recently Omalizumab, but use of other potentially useful medications is limited by lack of available studies (9, 10). Dapsone is a sulfone antibiotic with immunomodulatory properties which has shown promise in antihistamine refractory CIU, but to date has been limited by the evidence quality (6).

Dapsone's exact mechanism of action in CIU is unknown. However, a review of the anti-inflammatory effects of dapsone encompasses a variety of possible properties relevant to urticaria. These include interference with release or function of lysosomal enzymes and myeloperoxidase generation of toxic halides, disruption of integrin-mediated neutrophil adhesiveness, and inhibition of prostaglandin and leukotriene activity (11-14). This pilot study was designed to evaluate the efficacy of moderate dosed dapsone in antihistamine refractory CIU compared to placebo.

Methods

Study Design

This was a randomized, double-blinded, 6 week placebo-controlled treatment, crossover trial with a 2 week washout between treatments conducted at the General Clinical Research Center from February 2002 through July 2004 after approval by the University of Texas Southwestern Institutional Review Board. Patients were assessed every 3 weeks, after an

initial 1 week screening phase and the 2 week washout phase during the crossover, a total of 7 visits over the 15 week duration, shown in Figure I. The first visit was utilized to establish baseline lab studies, including complete blood counts, liver enzymes, renal function, and a pregnancy test, if appropriate. Complete blood counts were obtained on all subsequent visits and to ensure the study was unbiased the investigators who conducted visits were blinded to the blood count result.

After the first visit, patients were monitored for a 1 week screening period to confirm adequate urticaria activity (4 or more days' score of at least "1" for both hive and itch, on a 0 - 3 scale). During the next visit, used as the baseline, study subjects were randomized to either Dapsone-Placebo or Placebo-Dapsone, using a computer generated blocked randomization schema. They were given a 3 week supply of dapsone 100 mg orally or matching placebo, to be taken once daily. At the midpoint of the first phase of the trial, 3 weeks later, subjects received a 3-week refill to complete a total of 6 weeks of therapy. This was followed by a 2 week washout period during which patients took no study medication. They subsequently crossed over to receive 6 weeks of whichever medication was not taken during the initial phase. Subjects were instructed not to alter their existing medication or dietary regimens throughout the entire study, particularly if this included a fixed dose of corticosteroids. For safety and monitoring purposes, an investigator not involved in dispersing the medication was assigned to review blood counts.

Subjects

Men and women, aged 18 to 80, were eligible if they were diagnosed with CIU and had with hives and itching present at least 4 days in a week despite therapy in excess of standard H₁ antihistamine dosage, usually 2 to 4 times the standard dose, or simultaneous use of multiple H₁-antihistamines. 31% of subjects failed therapy with higher than licensed doses of single or multiple antihistamines while 69% had failed multiple concurrent antihistamines at licensed doses. For safety concerns patients were excluded on the basis of baseline anemia, hepatic disease, renal insufficiency, glucose-6-phosphate dehydrogenase (G6PD) deficiency, or pregnancy. Previous therapy with dapsone or concurrent skin diseases was also grounds for exclusion. Treatment with other second-line agents, including daily corticosteroids and leukotriene modifiers, was permitted as long as the dose and schedule was strictly unaltered for the entire duration of the study.

Assessments

Patients were required to keep daily diaries assessing both hive and itch severity. Each day they placed a score of "0" for no hives, "1" for 1 to 10 lesions, "2" for 11 to 50, and "3" for more than 50; simultaneously, a separate daily itch diary was scored "0" for none, "1" for mild pruritus, "2" for moderate, and "3" for severe. These daily scores were summed for a weekly diary score between 0 and 21, correlating to the weekly hive score (WHS) and weekly itch score (WIS). Additionally, on each of the 7 scheduled visits patients were assessed by questionnaires, which included a 10-cm unanchored visual analog scale (VAS) rating overall severity of urticaria, the Skindex-29 dermatologic quality of life (QOL) instrument, and the Medical Outcomes Study Short Form SF-12 (16). The Skindex-29 dermatologic (QOL) instrument, scaled from X - Y with lower values indicating

lower severity, assesses patients' perception of disease severity and its affect on function and emotion. The Medical Outcomes Study Short Form Survey SF-12, scaled from X - Y with lower values indicating lower severity, assesses the patients' perception of the disease' affect on physical and mental well being.

End Points

The co-primary endpoints were the change from baseline to week 6 in WHS and WIS, utilizing the 1-week screening period as the baseline for the WHS and WIS. Secondary endpoints analyzed were the VAS, Skindex-29, and SF-12 at baseline compared to week 6. The primary safety outcome measured was change in hemoglobin and hematocrit levels compared between dapsona and placebo. Upon completion of the trial we performed a post hoc analysis of the percent of patients with a 50% improvement in WHS and WIS along with the percent of patients with complete resolution of hives and itch.

Statistical Analysis

The study was designed to detect a 25% difference in the urticaria activity score between dapsona and placebo. We calculated that a sample size of $n=16$ after attrition was needed to detect this difference with 80% power at the 0.05 significance level and assuming 33% coefficient of variation. Mixed model repeated measures analysis was utilized to analyze this crossover design, which assessed the effect of treatment (dapsona versus placebo), the effect of treatment order, and the interaction between treatment and order. A statistically significant treatment x order interaction was observed, indicating a treatment carryover effect in our Dapsona-Placebo arm of the trial. Subsequently, we focused our analysis using the first treatment period only, analyzing these data as a parallel design using a mixed model analysis. Results are presented as a mean and standard deviation unless otherwise specified. Statistical analysis was performed using SAS version 9.2 (SAS Institute, Cary, North Carolina). A two-sided p-value < 0.05 was considered statistically significant.

Results

Figure II shows the number of patients who were screened and enrolled in the trial as well as the patients who completed the first arm of the trial. One patient in the dapsona arm failed to complete the first phase of the trial due to scheduling difficulty while all patients in the placebo arm completed the first phase. Additionally, three patients failed to cross over due to difficulty scheduling further visits and the final subject missed the final visit of the crossover phase. Baseline characteristics were similar in the two treatment order groups (Table I). The subjects were 77% female, age range from 25 - 64 years of age, and most patients had previously tried other agents for their urticaria, most commonly a leukotriene modifier, followed by an H₂ antihistamine, also shown in Table I. Most subjects had used bursts of corticosteroids previously, but only 1 was on a consistent dose throughout the entire study.

After the completion of the trial, we discovered a significant carryover effect where administration of the drug first causes continued symptom improvement in subsequent phases. The symptom improvement seen from dapsona was significantly greater than

placebo during the first arm, but this was not observed during the second arm, as seen in Figure III for weekly itch score. This carryover effect was statistically significant for WIS, WHS, and VAS ($p < 0.05$ for treatment x order interaction). The carryover effect may be directly related to an inadequate washout phase given the prolonged half-life of dapsone 12-30 hours and requiring 8-10 days to achieve steady state (13), or due to a disease modifying effect that persists in spite of the drug having been withdrawn.

Secondary to the carryover effect, only the data from the first phase of the trial was considered, changing the primary analysis of the study from a crossover to a parallel design. With the parallel design we analyzed the first phase of the P-D (Placebo) arm and the first phase of the D-P (Dapsone) arm. As shown in Figure IV and V for WHS and WIS respectively, after 6 weeks the patients in the dapsone arm showed a mean improvement over baseline in the co primary endpoints (mean [95% CI]) WHS (-3.5 [-6.2, -0.9] $p = 0.01$) and WIS (-4.8 [-7.6, -2.1] $p = 0.001$) while the placebo arm showed no statistically significant change from baseline. Additionally, a statistically significant improvement was seen by dapsone over placebo for WIS ($p = 0.047$) but not for WHS ($p = 0.16$). Shown in Table II, dapsone showed improvement over baseline for both VAS and Skindex – 29 but not SF-12 instrument, as well as a statistically difference between dapsone and placebo in VAS but not the Skindex-29 or SF-12 instrument.

A post hoc analysis to evaluate the percentage of patients with substantial clinical improvement was performed by looking at both phase 1 and 2 of the trial, at 3 and 6 weeks. Patients with clinically significant improvement would have 50%-99% improvement over baseline in WHS or WIS and complete responders would have a 100% resolution in hives and itch. We found that after six weeks on dapsone over 30% of patients had a 50% or greater improvement in WHS and WIS, 3 of whom were symptom free of both hive and itch. On placebo, no patients had a 50% or greater improvement.

Adverse events

No patients dropped out due to adverse effects. Adverse events occurring in the dapsone phase included mild nausea lasting several days in 2 subjects in the week 1, vaginal candidiasis in 1 subject in week 2, and mild neuropathy in 1 subject in week 6; viral respiratory infections occurred in 3 subjects during the placebo phase. A major concern of clinicians initiating dapsone therapy is the predictable, reversible decline in red blood cell count. Subjects in the dapsone arm of the study experienced a mean decline in hemoglobin of 1.8 mg/dL by week 3 from a mean baseline of 13.6, a 13.2% decline ($p = 0.001$) (Table III). The drop in hemoglobin was shown to be reversible and by the fifth week off the dapsone, the mean hemoglobin had risen to 13.7 mg/dL.

Discussion

Our study showed that daily dapsone at 100 mg per day had a significant improvement in symptoms. Our co-primary endpoints WIS and WHS were both statistically improved over baseline and WIS showed a significant improvement with dapsone over placebo. Additionally, of the 22 patients enrolled in the trial, 9 patients showed 50% improvement in WIS and 7 patients showed a 50% improvement in WHS with dapsone. In all

responders, efficacy was apparent within the first week. The placebo effect, traditionally thought to be substantial in the treatment of urticaria, was small and not statistically significant in this study. Whether this can be attributed to the crossover design or to other biases (e.g., fluctuating course with regression to the mean) is unclear. Ideally, the results of this pilot study should be confirmed with a larger trial; however, our study suggests that dapson was useful in limiting both hives and itch.

Dapsone (4,4'-diaminodiphenylsulfone), first used in the late-1940's for leprosy, is an orally administered sulfone with antimicrobial and anti-inflammatory properties (17, 18). One of dapson's first reported efficacy in CIU was described in 1978 by Matthews et al, in which a case of urticarial vasculitis was successfully treated by dapson (19). A series of 11 patients with severe relapsing CIU treated with dapson was published in 2005. Each patient was treated with dapson 25 mg/day plus cetirizine 10 mg/day and by 3 months, 9 of 11 patients obtained complete response; the final two achieved complete response after the dapson dose was increased to 50 mg/day (20). More recently, a non-blinded clinical trial showed that dapson in conjunction with an antihistamine was more efficacious than an antihistamine alone at controlling CIU with a persistent decrease in VAS and urticaria activity score (UAS) (21). In contrast to its role as an occasional salvage therapy for antihistamine refractory CIU, dapson is standard of care for a variety of dermatologic disorders.

Dapsone is considered first-line therapy for patients with dermatitis herpetiformis. Dapsone is usually started at 25 - 50 mg per day in conjunction with a gluten free diet, and then tapered to a maintenance dose of 1 mg/kg/day (17, 22, 23). Mucous membrane pemphigoid is another dermatologic condition where dapson is utilized as an alternative to systemic corticosteroids for mild to moderate disease (24, 25). Dapsone therapy is widely utilized in other dermatologic diseases as a first-line therapy for subcorneal pustular dermatosis, IgA pemphigus, and erythema elevatum diutinum and as an adjunct for cutaneous lupus erythematosus, pyoderma gangrenosum, and Behcet's disease (26-31). The efficacy seen by dapson in some dermatologic conditions does not guarantee its efficacy in chronic urticaria; additionally, prescribing physicians must be aware of its toxicities prior to initiating dapson.

The main adverse effect associated with dapson is anemia. On average, 80% of patients taking a daily dose of 100 - 150 mg dapson will have a drop of at least 1 g/dL in hemoglobin concentration (32, 33). Another common side effect of dapson is methemoglobinemia, a condition caused by physiologic ferrous (Fe^{2+}) heme iron oxidized to its ferric state (Fe^{3+}) (17). However, most patient with methemoglobinemia associated with dapson are asymptomatic and the effect resolves with cessation of the medication (17, 34). Dapsone is associated with other less common side effects including, hemolytic anemia due to G6PD deficiency, agranulocytosis, peripheral neuropathy, nephritis and hypothyroidism (35-38). Due to toxicities associated with dapson all patients should have complete blood counts, liver function tests and a G6PD prior to initiating therapy. Patients should be monitored monthly with complete blood counts and liver function tests for the first six months then periodically thereafter (38). The adverse effects of dapson are well known; however, in our trial they were minimal with no patients needing to drop out.

The goal of this pilot study was to generate wider recognition of the potential utility of this inadequately studied agent in the management of antihistamine refractory CIU. Potential limitations to this study are the small number of patients, the lack of follow up to evaluate long-term efficacy and the lack of detailed monitoring of antihistamine usage throughout the trial. However, the principle limitation in this study, which became apparent a posteriori, is the carryover effect. To counteract this, at the potential expense of statistical analysis, our analysis focused only on the first phase of trial. Future studies of dapsone in CIU may need to adopt a parallel design or a longer washout period. In this study, we observed that subjects who responded in the course of the study subsequently used less medication, while non-responders underwent a trial of “the next” second-line agent without delay. For appropriate patients, dapsone is an attractive medication with rapid benefit in those who respond, low cost, and the medications relatively familiarity amongst physicians.

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Bibliography

1. Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Gimenez-Arnau A, et al. EAACI/GA(2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy*. 2009; 64(10):1417–26. Epub 2009/09/24. [PubMed: 19772512]
2. O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. *The British journal of dermatology*. 1997; 136(2):197–201. Epub 1997/02/01. [PubMed: 9068731]
3. Khan DA. Chronic urticaria: diagnosis and management. *Allergy and asthma proceedings : the official journal of regional and state allergy societies*. 2008; 29(5):439–46. Epub 2008/10/18. [PubMed: 18926051]
4. Powell RJTG, Leech SC, Dixon TA, Clark AT, Mirakian R. BSACI guidelines for the management of chronic urticaria and angio-oedema. *Clinical and Experimental Allergy*. 2007; 37(2007):631–50. [PubMed: 17456211]
5. Greaves M. Chronic urticaria. *J Allergy Clin Immunol*. 2000; 105(4):664–72. Epub 2000/04/11. [PubMed: 10756214]
6. Maurer M, Weller K, Bindslev-Jensen C, Gimenez-Arnau A, Bousquet PJ, Bousquet J, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA(2)LEN task force report. *Allergy*. 2011; 66(3):317–30. Epub 2010/11/19. [PubMed: 21083565]
7. Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Gimenez-Arnau AM, et al. EAACI/GA(2)LEN/EDF/WAO guideline: management of urticaria. *Allergy*. 2009; 64(10):1427–43. Epub 2009/09/24. [PubMed: 19772513]
8. Kaplan AP. Clinical practice. Chronic urticaria and angioedema. *The New England journal of medicine*. 2002; 346(3):175–9. Epub 2002/01/18. [PubMed: 11796852]
9. Trojan TD, Khan DA. Calcineurin inhibitors in chronic urticaria. *Current opinion in allergy and clinical immunology*. 2012; 12(4):412–20. Epub 2012/06/26. [PubMed: 22729026]
10. Kaplan A, Ledford D, Ashby M, Canvin J, Zazzali JL, Conner E, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *Journal of Allergy and Clinical Immunology*. 2013; 132:101–109. [PubMed: 23810097]

11. Maurer M, Rosen K, Hsieh HJ, Saini S, Grattan C, Gimenez-Arnau A, et al. Omalizumab for the Treatment of Chronic Idiopathic or Spontaneous Urticaria. *The New England journal of medicine*. 2013; 368(24):2340–1. Epub 2013/02/26.
12. Bonney RJ, Wightman PD, Dahlgren ME, Sadowski SJ, Davies P, Jensen N, et al. Inhibition of the release of prostaglandins, leukotrienes and lysosomal acid hydrolases from macrophages by selective inhibitors of lecithin biosynthesis. *Biochemical pharmacology*. 1983; 32(2):361–6. Epub 1983/01/15. [PubMed: 6553500]
13. Bozeman PM, Learn DB, Thomas EL. Inhibition of the human leukocyte enzymes myeloperoxidase and eosinophil peroxidase by dapsone. *Biochemical pharmacology*. 1992; 44(3): 553–63. Epub 1992/08/04. [PubMed: 1324677]
14. Booth SA, Moody CE, Dahl MV, Herron MJ, Nelson RD. Dapsone suppresses integrin-mediated neutrophil adherence function. *The Journal of investigative dermatology*. 1992; 98(2):135–40. Epub 1992/02/01. [PubMed: 1732379]
15. Wozel G, Lehmann B. Dapsone inhibits the generation of 5-lipoxygenase products in human polymorphonuclear leukocytes. *Skin pharmacology : the official journal of the Skin Pharmacology Society*. 1995; 8(4):196–202. Epub 1995/01/01. [PubMed: 7488396]
16. Chren MM, Lasek RJ, Flocke SA, Zyzanski SJ. Improved discriminative and evaluative capability of a refined version of Skindex, a quality-of-life instrument for patients with skin diseases. *Archives of dermatology*. 1997; 133(11):1433–40. Epub 1997/11/26. [PubMed: 9371029]
17. Zhu YI, Stiller MJ. Dapsone and sulfones in dermatology: overview and update. *Journal of the American Academy of Dermatology*. 2001; 45(3):420–34. Epub 2001/08/21. [PubMed: 11511841]
18. Lorenz M, Wozel G, Schmitt J. Hypersensitivity reactions to dapsone: a systematic review. *Acta dermato-venereologica*. 2012; 92(2):194–9. Epub 2012/02/07. [PubMed: 22307940]
19. Matthews CN, Saihan EM, Warin RP. Urticaria-like lesions associated with systemic lupus erythematosus: response to dapsone. *The British journal of dermatology*. 1978; 99(4):455–7. Epub 1978/10/01. [PubMed: 708619]
20. Cassano N, D'Argento V, Filotico R, Vena GA. Low-dose dapsone in chronic idiopathic urticaria: preliminary results of an open study. *Acta dermato-venereologica*. 2005; 85(3):254–5. Epub 2005/07/26. [PubMed: 16040414]
21. Engin B, Ozdemir M. Prospective randomized non-blinded clinical trial on the use of dapsone plus antihistamine vs. antihistamine in patients with chronic idiopathic urticaria. *Journal of the European Academy of Dermatology and Venereology : JEADV*. 2008; 22(4):481–6. Epub 2007/12/18. [PubMed: 18081753]
22. Mutasim DF. Management of autoimmune bullous diseases: pharmacology and therapeutics. *Journal of the American Academy of Dermatology*. 2004; 51(6):859–77. quiz 78-80. Epub 2004/12/08. [PubMed: 15583576]
23. Gordon RA, Mays R, Sambrano B, Mayo T, Lapolla W. Antibiotics used in nonbacterial dermatologic conditions. *Dermatologic therapy*. 2012; 25(1):38–54. Epub 2012/05/18. [PubMed: 22591498]
24. Kirtschig G, Murrell D, Wojnarowska F, Khumalo N. Interventions for mucous membrane pemphigoid and epidermolysis bullosa acquisita. *Cochrane Database Syst Rev*. 2003; 1:CD004056. Epub 2003/01/22. [PubMed: 12535507]
25. Knudson RM, Kalaaji AN, Bruce AJ. The management of mucous membrane pemphigoid and pemphigus. *Dermatologic therapy*. 2010; 23(3):268–80. Epub 2010/07/06. [PubMed: 20597945]
26. Reed J, Wilkinson J. Subcorneal pustular dermatosis. *Clinics in dermatology*. 2000; 18(3):301–13. Epub 2000/06/17. [PubMed: 10856662]
27. Yasuda H, Kobayashi H, Hashimoto T, Itoh K, Yamane M, Nakamura J. Subcorneal pustular dermatosis type of IgA pemphigus: demonstration of autoantibodies to desmocollin-1 and clinical review. *The British journal of dermatology*. 2000; 143(1):144–8. Epub 2000/07/25. [PubMed: 10886149]
28. Kuhn A, Ruland V, Bonsmann G. Cutaneous lupus erythematosus: update of therapeutic options part I. *Journal of the American Academy of Dermatology*. 2011; 65(6):e179–93. Epub 2010/08/27. [PubMed: 20739095]

29. Paramkusam G, Meduri V, Gangeshetty N. Pyoderma gangrenosum with oral involvement - case report and review of the literature. *International journal of oral science*. 2010; 2(2):111–6. Epub 2010/08/27. [PubMed: 20737938]
30. Hasselmann DO, Bens G, Tilgen W, Reichrath J. Pyoderma gangrenosum: clinical presentation and outcome in 18 cases and review of the literature. *Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG*. 2007; 5(7):560–4. Epub 2007/07/06. [PubMed: 17610605]
31. Lin P, Liang G. Behcet disease: recommendation for clinical management of mucocutaneous lesions. *Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases*. 2006; 12(6):282–6. Epub 2006/12/07. [PubMed: 17149058]
32. Byrd SR, Gelber RH. Effect of dapsone on haemoglobin concentration in patients with leprosy. *Leprosy review*. 1991; 62(2):171–8. Epub 1991/06/01. [PubMed: 1870379]
33. Grindulis KA, McConkey B. Rheumatoid arthritis: the effects of treatment with dapsone on hemoglobin. *The Journal of rheumatology*. 1984; 11(6):776–8. Epub 1984/12/01. [PubMed: 6520831]
34. Barclay JA, Ziemba SE, Ibrahim RB. Dapsone-induced methemoglobinemia: a primer for clinicians. *The Annals of pharmacotherapy*. 2011; 45(9):1103–15. Epub 2011/08/20. [PubMed: 21852596]
35. Coleman MD. Dapsone-mediated agranulocytosis: risks, possible mechanisms and prevention. *Toxicology*. 2001; 162(1):53–60. Epub 2001/04/20. [PubMed: 11311458]
36. Hornsten P, Keisu M, Wiholm BE. The incidence of agranulocytosis during treatment of dermatitis herpetiformis with dapsone as reported in Sweden, 1972 through 1988. *Archives of dermatology*. 1990; 126(7):919–22. Epub 1990/07/01. [PubMed: 2360840]
37. Kosseifi SG, Guha B, Nassour DN, Chi DS, Krishnaswamy G. The Dapsone hypersensitivity syndrome revisited: a potentially fatal multisystem disorder with prominent hepatopulmonary manifestations. *J Occup Med Toxicol*. 2006; 1:9. Epub 2006/06/08. [PubMed: 16756657]
38. Bernstein JA, Lang DM, Khan DA, Craig T, Dreyfus D, Hsieh F, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol*. 2014; 133(5): 1270–1277.10.1016/j.jaci.2014.02.036 [PubMed: 24766875]

Abbreviations

CIU	Chronic Idiopathic Urticaria
VAS	Visual Analog Scale
WHS	Weekly Hive Score
WIS	Weekly Itch Score
WUS	Weekly Urticaria Score
QOL	Quality of Life
G6PD	Glucose-6-phosphate dehydrogenase
DH	Dermatitis Herpetiformis
UAS	Urticaria Activity Score
SD	Standard Deviation

Highlights

What is already known about the topic?

Chronic Idiopathic Urticaria is a common disease with a large societal impact. While H₁-antihistamines are the mainstay of treatment, many patients will have an incomplete response and are faced limited options.

What does this article add to our current knowledge?

Quality evidence is lacking for many of the medications utilized in antihistamine refractory CIU. This trial lends more credible evidence that dapsone is an efficacious tool for CIU in patients who tolerate it.

How does this study impact current management guidelines?

This trial supports dapsone's role as a viable medication in antihistamine refractory CIU

Figure I. Study design

Figure II. Study flow diagram

Figure III. Treatment-Order interaction shown for weekly itch score over 14 weeks Dapsone (filled symbols), Placebo (open symbols)

Figure IV.

Dapsone versus placebo in weekly hive score over time.

Dapsone (filled symbols), Placebo (open symbols)

Figure V.

Dapsone versus placebo in weekly itch score over time.

Dapsone (filled symbols), Placebo (open symbols)

Table I
Baseline Characteristics

Characteristics	P – D Placebo Arm	D – P Dapsone Arm	All Patients
No. of Patients	12	10	22
Completed [¶]	11 (92%)*	7 (70%)	18 (82%)*
Dropped Out [¶]	1 (8%)	3 (30%)	4 (18%)
Male : Female	3 : 9	2 : 8	5 : 17
Age (yr): Range	44.8 (13.9) 25–64	41.9 (11.0) 25–64	43.5 (12.4) 25–64
Ethnicity			
White : Hispanic : Asian	10 : 2 : 0	9 : 0 : 1	19 : 2 : 1
Duration of Urticaria (yr): Median, Range	1.3 0.3–10	1.0 0.5–5	1.0 0.3–10
WHS	13.6 (5.0)	13.4 (5.1)	13.5 (4.9)
WIS	12.8 (3.8)	12.5 (4.9)	12.7 (4.2)
VAS	3.7 (2.0)	4.4 (2.5)	4.0 (2.2)
Hemoglobin (mg/dL)	13.7 (0.8)	13.6 (1.3)	13.6 (1.3)
Hematocrit	40.1 (2.2)	40.5 (3.1)	40.3 (2.6)
Prior Failed Treatments, n (%)			
H ₁ Antihistamines Only	3 (25%)	0 (0%)	3 (13.6%)
H ₂ Antihistamine	4 (33.3%)	7 (70%)	11 (50%)
Leukotriene Modifier	9 (75%)	7 (70%)	16 (72.7%)
Thyroxine	0 (0%)	1 (10%)	1 (4.5%)
Colchicine	0 (0%)	1 (10%)	1 (4.5%)
Methotrexate	0 (0%)	1 (10%)	1 (4.5%)
Azathioprine	1 (8.3%)	0 (0%)	1 (4.5%)
Chinese Herbs	0 (0%)	1 (10%)	1 (4.5%)

WHS, weekly hives score; WIS, weekly itch score; VAS, visual analog scale

Variables are summarized as mean (SD) unless otherwise indicated.

* Includes one patient for whom the second 3 weeks of crossover data are not available.

[¶] All patients completed the first phase of the trial and were analyzed in the parallel design

Six-week results of dapsonе versus placebo

	Dapsone, n=10			Placebo, n=12		
	<u>Week 0</u>	<u>Week 6</u>	<u>Baseline versus Week 6 p-value</u> *	<u>Week 0</u>	<u>Week 6</u>	<u>Baseline Versus Week 6 p-value</u> *
WHS	13.4 (5.1)	10 (8.1)	0.02	13.6 (5)	13.4 (3.8)	0.88
WIS	12.5 (4.9)	7.7 (7.4)	0.001	12.8 (3.8)	11.9 (2.9)	0.68
VAS	4.4 (2.5)	6.6 (3.1)	0.01	3.7 (2)	3.4 (2.3)	0.93
Skindex Emotion	41.3 (13)	28.4 (18)	0.01	40.6 (21.3)	34.4 (17.9)	0.13
Skindex Function	30.6 (16.1)	16.4 (15.7)	0.005	31.4 (17.8)	27.8 (19.5)	0.52
Skindex Symptoms	37.9 (13.9)	22.3 (18.3)	0.03	34.8 (15.7)	35.1 (21)	0.98
SF-12 Physical	52.3 (5.9)	53.5 (5.7)	0.87	44.9 (10.4)	46.5 (9.9)	0.47
SF-12 Mental	49.8 (4.4)	51.3 (1.6)	0.66	50.5 (4.6)	49.7 (5)	0.79

WHS, Weekly Hive Score; WIS – Weekly Itch Score; VAS – Visual Analog Score; SF – Short Form

* Comparison between baseline and week 6 within the dapsons and placebo groups

^aComparison between dapstone and placebo group response over timer (interaction effect)

Results are represented as Mean (Standard Deviation)

Table III
Mean change in hemoglobin and hematocrit with dapsone and placebo

Red Cell Index	* Dapsone, n=10			Placebo, n=12		
	Week			Week		
	0	3	6	0	3	6
Hemoglobin (mg/dL) [¶]	13.6 (1.3)	11.8 (1.2)	11.6 (1.4)	13.7 (0.8)	13.3 (0.8)	13.2 (1.0)
Hematocrit [¶]	40.5 (3.1)	34.8 (3.6)	34.6 (4.0)	41.1 (2.2)	39.1 (1.9)	38.8 (2.9)

* Both Hemoglobin and Hematocrit fell at 3 weeks (p<0.001) on dapsone but then stabilized with no further, significant drop

[¶]Values shown as mean (standard deviation)