Methotrexate versus Acitretin in the Treatment of Chronic Hand Dermatitis

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Background: Recent studies have produced treatment algorithms for hand dermatitis, but there are limited current indications of systemic treatments for chronic hand dermatitis.

Objective: To compare the efficacy and safety of methotrexate and acitretin in the treatment of chronic hand dermatitis.

Methods: A chart-retrospective review of all patients with hand dermatitis seen by the primary author at the University of North Carolina Dermatology and Skin Cancer Center from September 2007 to April 2013.

Results: Eighty-three hand dermatitis charts were reviewed. Twenty-nine patients received systemic therapy, of which 17 (26.5%) were treated systemically with acitretin and/or methotrexate. Of these 17 patients, four patients received courses of both acitretin and methotrexate independently after failing the alternative treatment course. At 6 months, acitretin achieved clearance/almost clearance in 44% of patients, compared to 0% of those treated with methotrexate. At 12 months, 100% of patients treated with acitretin achieved clearance/almost clearance compared to 40% of patients treated with methotrexate. Adverse effects were minimal and as expected.

Limitations: This was a retrospective study, and the small sample size makes it difficult to generalize results.

Conclusion: Systemic retinoids are a good alternative for the treatment of chronic hand dermatitis.

Introduction

Chronic hand dermatitis (CHD) is an inflammatory condition of the skin, often with a multifactorial cause[1] of environmental and genetic factors. It is a chronic, relapsing skin disease,[2] with a point prevalence around 4%, and a lifetime prevalence >15%.[3] There is no consensus about the treatment of CHD and current conventional therapies include avoidance of irritants and potential allergens, thick emollients, topical corticosteroids and topical immunomodulators. Severe cases often require systemic therapies such as oral steroids and systemic immunosuppressants.[2] The purpose of this study was to retrospectively review the charts of patients with CHD seen in a tertiary center and describe the efficacy and safety of methotrexate and acitretin.

Methods

This is a chart-retrospective review of all patients with CHD seen from September 2007 to April 2013 by the primary author at the University of North Carolina (UNC) Dermatology Clinic. Patients with fungal, viral, and bacterial infections were excluded. Due to the retrospective nature of the study, clinical variants of CHD were not identified. The Institutional Review Board at UNC-Chapel Hill approved the study.

All patients treated with a systemic agent were identified and demographics, medical history, laboratories, systemic agent used, time to see improvement, time to achieve a clear or almost clear response and side effects were collected. Response to therapy was graded on a 3-point scale: 0 corresponded to no change or worsening from baseline; 1 corresponded to improvement of fissuring, erythema, and/or desquamation; and 2 corresponded to resolution of erythema, fissuring, and desquamation, or presence of only mild desquamation or erythema. The same investigator evaluated all patients. The follow up period varied from 4 to 39 months.

Data was calculated using a Student *t* test, 2-sided, type 3 (two sample, unequal variance). Test results were interpreted as statistically significant for *P* values less than or equal to .05.

Results

A total of 83 charts were reviewed, from which twenty-nine (34.9%) required systemic treatment, including oral prednisone, dapsone, acitretin, and methotrexate. Seventeen (26.5%) were treated systemically with acitretin and/or methotrexate. Demographics of these 17 patients include 12 (70.6%) males and five (29.4%) females with a mean age of 53 (32-71) years. Of these 17 patients, four patients were treated with both acitretin and methotrexate at different times. Three patients failed methotrexate and were switched to acitretin, and one patient relapsed on acitretin at 15 months and was switched to methotrexate.

Acitretin was significantly better than methotrexate to cause a clear or almost clear response in patients with CHD by 6 months (P = 0.0353, see Table 1). The four patients receiving both were considered unique subjects for each treatment. Only 6 patients on acitretin and 5 patients on methotrexate maintained follow-up through 12 months. One hundred percent of patients on acitretin and 40% of patients on methotrexate were clear or almost clear (P = 0.0705) at 12 months follow-up. Mean time to show improvement was not significantly different for both treatments, (2.28 months for acitretin versus 2.75 for methotrexate) but it was significant for mean time to achieve clearance (6.78 months for acitretin versus 12.8 for methotrexate). Adverse effects were minimal and as expected and are summarized in Table II.

Discussion

Chronic hand dermatitis (CHD) is not a uniform disease because of differences in etiology, morphology, and severity.[4,5] The chronicity and variable presentation makes treatment difficult.

Some studies have reviewed the therapeutic options available for CHD and proposed treatment algorithms but there are very few clinical trials providing evidence of efficacy of systemic drugs. In a previous large phase III trial, 47.7% of patients with severe CHD who received alitretinoin 30 mg achieved full clinical response, defined as 'clear' or 'almost clear' hands, within 200 days.[6] This study paved the way for the approval of oral

TABLE 1.

Comparison of Patient Response to Acitretin (with or without Methotrexate) Versus Methotrexate Without Acitretin			
	Acitretin, n=9	Methotrexate, n=12	*P*-values
Average Follow-Up, mo	16	14.33	
Average Patient Dose	27.46 mg/d	12.79 mg/week	
Mean Time to Show Improvement, mo	2.28	2.75	0.5193
% Clear or Almost Clear at 6 mo	44%	0%	0.0353
Mean Time to Clear, mo	6.78	12.8	0.1091
% Clear or Almost Clear, 12 mo	100% (n=6)	40% (n=5)	0.0705
% Clear or Almost Clear, Total	100%	41.70%	

alitretinoin for hand dermatitis in most of Europe and Canada in 2008, and it remains the only licensed systemic treatment for hand dermatitis. In 2012, Diepgen et al investigated the use of alitretinoin to treat CHD under daily "real life" medical practice conditions in Germany. In total, 56.7% of patients achieved a clear or almost clear response, with only small differences in patients with different morphological forms: hyperkeratotic-rhagidiform (59.2%), fingertip (52.2%), and vesicular (47.9%).[7] Recently, Fowler et al reported that 40% of patients treated with alitretinoin 30 mgs daily achieved a clear or almost clear response after 24 weeks of treatment.[8] Alitretinoin is not currently licensed for use in the United States.

In view of these results, we treated some of our patients with acitretin, a retinoid available in the United States. Acitretin inhibits the expression of pro-inflammatory cytokines interleukin-6 (IL-6), migration inhibitory factor-related protein-8 (MRP-8), and interferon-gamma (markers of hyperproliferation and abnormal keratinocyte differentiation). It acts as an anti-inflammatory and antiproliferative, resulting in keratinocyte differentiation and normalization of the epithelium.[9-11] This combination of anti-inflammatory and antiproliferative effects explains one possible mechanism for the success of acitretin in treatment of the hyperkeratotic variant.

For all CHD patients treated with acitretin (with or without methotrexate), we noted statistically significant responses compared to methotrexate (without acitretin) at 6 months (*P* = 0.0353). Although the sample was small, a better response to acitretin was also noted at 12 months. (Table 2) The doses of acitretin and methotrexate varied among patients based on safety, tolerability, and efficacy considerations. The response can be relatively slow, with 3 to 6 months required to achieve a maximal response.[12] The average patient dose was 27.46 mg/d for acitretin and 12.79 mg/week for methotrexate.

TABLE 2.

Adverse Effects Experienced During Treatment		
Adverse Effect	Acitretin, n=9	Methotrexate, n=12
Hair Loss	1	0
Dryness	1	1
Elevated Non-fasting Cholesterol, n (min-max)	5 (201-278)	4 (208-370)
Elevated Non-fasting Triglycerides, n (min-max)	9 (171-563)	3 (198-244)
Elevated ALT/AST, n (min-max)	2 (ALT: 74-76, AST: 98)	1 (ALT: 92)

Adverse effects are summarized in Table 2. These adverse effects are comparable to those described by Dunn et al. in a literature review of acitretin in 2011.13 Although a majority of patients experienced abnormal laboratory values, none were severe enough to require discontinuation. Hypertriglyceridemia was successfully managed through dietary modifications or dose reductions.

Acitretin should not be used in women of childbearing potential unless other treatment options are exhausted and the benefits outweigh the risks. When its use is merited, contraception must be used and pregnancy must be avoided for three years due to the potential conversion of acitretin to etretinate.[14] In this study, there were no female patients of childbearing potential treated with acitretin.

We believe that acitretin merits further clinical evaluation regarding its efficacy in CHD patients, and it should potentially be the drug of choice for patients with CHD.

Study limitations include UNC serving as a referral center for many of these patients with CHD, small sample size, selection bias in evaluating patients for different treatments, and selection bias due to treatment potential in females with childbearing potential.

Disclosure

The authors have no conflict of interest to declare.

References

1. 1: Coenraads PJ. Hand eczema. *N Engl J Med.* 2012;367(19):1829-37.
2. 2: Sohn A, Frankel A, Patel RV, Goldenberg G. Eczema. *Mt Sinai J Med.* 2011;78(5):730-9.
3. 3: Thyssen JP, Johansen JD, Linneberg A, Menné T. The epidemiology of hand eczema in the general population–prevalence and main findings. *Contact Dermatitis.* 2010;62(2):75-87.
4. 4: Bissonnette R, Diepgen TL, Elsner P, English J, Graham-Brown R, Homey B, et al. Redefining treatment options in chronic hand eczema (CHE). *J Eur Acad Dermatol Venereol.* 2010;24 Suppl 3:1-20.
5. 5: Golden S, Shaw T. Hand Dermatitis: Review of Clinical Features and Treatment Options. *J Cutan Med Surg.* 2013;32(3):147-57.

6. 6: Ruzicka T, Lynde CW, Jemec GB, Diepgen T, Berth-Jones J, Coenraads PJ, et al. Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. *Br J Dermatol*. 2008;158(4):808-17.
7. 7: Diepgen TL, Pfarr E, Zimmermann T. Efficacy and tolerability of alitretinoin for chronic hand eczema under daily practice conditions: results of the TOCCATA open study comprising 680 patients. *Acta Derm Venereol*. 2012;92(3):251-5.
8. 8: Fowler JF, Graff o and Hamedani AG. A Phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of alitretinoin (BAL4079) in the treatment of severe chronic hand eczema refractory to potent topical corticosteroid therapy. *J Drugs Dermatol*. 2014;13 (10):1198-1204.
9. 9: Saurat JH. Retinoids and psoriasis: novel issues in retinoid pharmacology and implications for psoriasis treatment. *J Am Acad Dermatol*. 1999;41(3 Pt 2):S2-6.
10. 10: Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. *J Am Acad Dermatol*. 2009;61(3):451-85.
11. 11: DiSepio D, Malhotra M, Chandraratna RA, Nagpal S. Retinoic acid receptor-nuclear factor-interleukin 6 antagonism: A novel mechanism of retinoid-dependent inhibition of a keratinocyte hyperproliferative differentiation marker. *J Biol Chem*. 1997;272(41):25555-9.
12. 12: Capella GL, Fracchiolla C, Frigerio E, Altomare G. A controlled study of comparative efficacy of oral retinoids and topical betamethasone/salicylic acid for chronic hyperkeratotic palmoplantar dermatitis. *J Dermatolog Treat*. 2004;15(2):88-93.
13. 13: Dunn LK, Gaar LR, Yentzer BA, O'Neill JL, Feldman SR. Acitretin in dermatology: a review. *J Drugs Dermatol*. 2011 Jul;10(7):772-82.
14. 14: Soriatane (acitretin) prescribing information. Stiefel Laboratories, Inc. Available at: http://www.soriatane.com/about-soriatane.html. Accessed August 11, 2013.

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