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Is Alitretinoin (9-*cis*-retinoic acid) Safe And Effective For Use In Hand Eczema?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVE: To determine if Alitretinoin is a safe and effective alternative to current treatments in reducing the symptoms of Hand Eczema (HE)

STUDY DESIGN: Review of all English language primary double-blind randomized controlled trial studies and an exploratory open-label case series from 1999-2009

DATA SOURCES: An exploratory open-label case series comparing Alitretinoin at various dosages and randomized, controlled, double-blind clinical trials comparing Alitretinoin to placebo. All sources were found using PubMed and Cochrane databases.

OUTCOME MEASURED: The open-label case series was a pilot study where the treating physician measured erythema, papules/vesicles, desquamation, hyperkeratosis, rhagades and pruritus/pain on a 4-point scale from 0(no symptoms) to 4(severe symptoms). Participants were evaluated monthly for 1-5 months, depending on how well each participant tolerated treatment. The randomized, controlled, double-blind clinical trials measured the modified Total Lesion Symptom Score (mTLSS), which measured the intensity of seven individual symptoms of chronic hand eczema: erythema, scaling, lichenification/hyperkeratosis, vesiculation, oedema, fissures, and pruritus/pain. Participants of these studies were evaluated for each symptom with a score of 0(no signs or symptoms) to 3(severe symptoms) at baseline, twelve weeks, and twenty-four weeks.

RESULTS: The open-label case series by Bollag found oral Alitretinoin to be very efficacious in the treatment of HE. The two double-blind randomized controlled trials, by Ruzicka and Bissonnette, indicate significant results using oral Alitretinoin. Results showed Alitretinoin induces clinically significant responses in a high percentage of patients with severe chronic hand eczema as both initial treatment as well as subsequent treatment for HE refractory to initial treatment with Alitretinoin. Participants in all studies experienced only mild side effects from treatment, the most common of which was headache.

CONCLUSIONS: The results of these studies show that use of oral Alitretinoin given at individually well-tolerated doses (30-40 mg) induces clearing of HE in a substantial proportion of patients with severe disease refractory to standard corticosteroid therapy as well as HE refractory to treatment with a previous course of Alitretinoin. Additionally, these studies show that Alitretinoin can be used safely as intermittent treatment for long-term management of HE.

KEY WORDS: Alitretinoin, Hand Eczema

INTRODUCITON

Hand eczema (HE) is the most common dermatosis that affects the hands and many patients suffer from the condition chronically despite avoidance of causative agent(s). The current treatment for HE is long-term use of topical corticosteroids. However, even with this treatment patients experience decreased response over time, rebound flares, and overall lack of improvement.¹ This paper evaluates two randomized controlled clinical trials that compare doses of 10 mg and 30 mg oral treatments of Alitretinoin to placebo. Additionally evaluated is one open-label case series which compares multiple dosing regimens and tapers. All studies were conducted in an effort to decrease symptoms of patients suffering from HE and improve long-term management.

HE affects 7-12% of the general population of Northern Europe and is estimated to affect an even higher percentage of the population in the United States. Of the patients diagnosed with HE, 5-7% of them usually develop chronic hand eczema (CHE). There are many irritants, allergens, and exogenous factors that exacerbate HE, making it difficult to identify all triggers of the dermatosis. In severe cases, HE can cause occupational disability if the use of hands plays a key role in performing a job. HE can also cause psycho-social disability as the condition can cause substantial disfiguring of the hands.² In the Netherlands, annual costs of medical care, absenteeism, and disability pensions due to occupational skin disease in employees in 2001 were estimated at € 98.1 million (equivalent = \$132 million). There are currently no estimates for the number of healthcare visits per year for HE.¹⁻³

A specific cause of HE is unknown but it is hypothesized to be multifactorial. This condition is characterized by pruritis, which leads to erythema, vesiculation, scaling, lichenification, hyperkeratosis, blistering, fissures, and pain. The long-term prognosis is

poor. Current therapies include skin protection practices (i.e. gloves), lifestyle changes to avoid irritants, use of emollients, and topical corticosteroids. Despite these treatments, many patients suffer chronically. Because the efficacy of topical corticosteroids tends to decline over time, there is a great push to find a treatment that has consistent results with long-term use. Retinoids are known to affect keratinization & inflammation. Alitretinoin is a retinoid that binds to all six retinoid receptors in contrast to tretinoin, acitretin, and retinoic acid which have less binding capacity. Previous studies have shown topical Alitretinoin (Panretin®) to be beneficial for AIDS patients with skin lesions from Kaposi sarcoma. Current research is hopeful that Alitretinoin will have a similar beneficial effect on the skin for individuals suffering from HE.^{1,4,5}

OBJECTIVE:

The objective of this systematic review is to determine whether or not "Is Alitretinoin (9-*cis*-retinoic acid) safe & effective for use in Hand Eczema?" The hypothesis about the objective is that Alitretinoin given at well-tolerated doses is effective and an acceptable long-term treatment in clearing HE in patients with severe disease refractory to standard corticosteroid therapy.

METHODS:

A detailed search was completed by the author, using search engines PubMed and Cochrane Database of Systematic Reviews. The key words "Alitretinoin" and "Hand Eczema" were used in combination to search for English articles and all of the resulting articles were published in peer-review journals from 1999-2009. The articles were selected based on the importance of outcomes to patient (Patient Oriented Evidence that Matters, or POEMS). Studies that were included were those that were randomized, controlled, prospective, and were based on a patient-oriented outcome. Excluded studies were those that used Alitretinoin as treatment for

diseases other than HE. Randomized controlled trials (RCTs) were searched for those with a patient population between 16 and 75 y.o. with clinically diagnosed HE that was refractory to standard corticosteroid treatment. Only RCTs that compared treatment groups receiving oral Alitretinoin compared to a placebo group were considered. In addition, one exploratory open-label case series compared multiple dosing regimens of Alitretinoin for tolerance and effectiveness.⁵ Under these criteria, two double-blind, randomized, placebo-controlled clinical trials and one open-label case series were identified and are included in this review. Table 1 includes demographics of the included studies. The two RCT studies reported statistics based on numerical severity scores of CHE symptoms. Statistics reported or used include *p*-values with a value of <0.05 being statistically significant.^{1-2,5}

OUTCOMES MEASURED

Outcomes of the studies by Ruzicka and Bissonnette were measured by severity categorization, which corresponded to the intensity of HE symptoms. Severity was defined according to the Physician Global Assessment (PGA) whereby seven symptoms are evaluated using the modified Total Lesion Symptom Score (mTLSS). The mTLSS addressed erythema, scaling, lichenification/hyperkeratosis, vesiculation, edema, fissures, and pruritis/pain. PGA categories were based on the mTLSS and ranged from “clear” to “severe.” Among the seven total symptoms being addressed, qualifications were as follows: Clear- no symptoms; undetectable, Almost Clear- at least one mild symptom/absent affecting <10% of hand surface, Mild- at least one mild symptom affecting <10% of hand surface, Moderate- at least one mild or moderate symptom affecting 10-30% of hand surface, Severe- at least one moderate or severe symptom affecting >30% of hand surface. Participants were given a score for each of the seven symptoms that, when added together, determined the PGA score. The scoring for each of the mTLSS symptoms rated on a scale from 0-3 where 0= no symptoms, 1=mild, 2=moderate, and

3=severe symptoms. The criteria for the scoring of each symptom is as follows: Erythema 0-absent, 1- faint, 2-prominent redness, 3-deep intense red color, Scaling 0-absent, 1- slight flaking over limited areas/mostly fine scales, 2- flaking over widespread areas(s)/coarser scales, 3-desquamation covering over 30% of hand with coarse thick scales, Lichenification/Hyperkeratosis 0- absent, 1- mild thickening with exaggerated skin lines over limited areas, 2- palpable thickening over widespread areas, 3- prominent thickening over widespread areas with exaggeration of normal skin markings, Vesiculation 0- absent, 1- scattered vesicles affecting up to 10% of hand without erosion, 2- scattered or clustered vesicles affecting up to 30% of hand without erosion or excoriation, 3- high density of vesicles extending over large areas(s), or with erosion or excoriation, Edema 0- absent, 1- dermal swelling over less than 10% of hands, 2- definite dermal swelling over more than 10% of hand, 3- dermal swelling with skin induration over widespread areas(s), Fissures 0- absent, 1- cracked skin affecting a small area of the hand, cracked skin affecting multiple areas of the hand & causing pain, 3- one or more deep fissures and causing bleeding or severe pain, Pruritus/Pain 0- absent, 1- occasional, slight discomfort a few times per day, 2- intermittent, causing discomfort frequently during the day, 3- persistent or interfering with sleep.¹⁻²

Bollag evaluated slightly different CHE symptoms: erythema, papules/vesicles, desquamation, hyperkeratosis, rhagades, and pruritus/pain, which were rated on a 0-4 point scale where 0- none, 1- slight, 2-moderate, 3-marked, 4-severe. These scores were based on a subjective assessment by the treating physician on the correlation between Therapeutic Response (TR) and the Reduction of the Total Lesion/Symptom Score (rTLSS). The rTLSS was recorded as a percentage that corresponded to a categorization of TR such that 0-20%- no therapeutic response, 21-40%- slight response, 41-60%- moderate response, 61-80%- good response, 81-100%- very good response.⁵

Table 1. Characteristics of studies included in systematic review of the safety & effectiveness of Alitretinoin (9-*cis*-retinoic acid) for use in Hand Eczema

Study	Type	#Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Bissonnette, CANADA 2009	Double-blind, placebo controlled, RCT	117	49-52	BACH participants who rated as "clear" or "almost clear" hands according to PGA at termination of treatment, but then relapsed within 24 weeks	immunosuppressants used within last 4 weeks drugs with potential interactions (i.e. systemic azoles, erythromycin, clarithromycin, simvastatin, St. John's wort) within last 2 weeks, use of concomitant retinoids (oral or topical to hands), vitamin supplements with > 2000 IU Vit. A	24	Alitretinoin 10 mg or 30 mg po QD x 12-24 weeks
Bollag, SWITZERLAND 1999	Open label, Case Series	38	16-85	Patients with CHE refractory to conventional therapy; emphasis on hyperkeratotic palmar eczema	N/A	0	Alitretinoin 20 mg or 40 mg po x 1-5 months
Ruzicka, GERMANY 2008	Double-blind, placebo controlled, prospective, multicentre RCT	1032	18-75	18-75 y.o. and diagnosed with any type of severe hand eczema (CHE) of at least 6 months refractory to standard topical corticosteroid therapy	Diagnosis of psoriasis, atopic dermatitis treated with prescription drugs, active bacterial/fungal/viral infection of hands, or allergic contact dermatitis of hands with unavoidable exposure to allergen, or other skin diseases likely to interfere with the study Use of concomitant retinoids (oral or topical to hands), vitamin supplements with > 2000 IU Vitamin A	273	Alitretinoin 10 mg or 30 mg po QD x up to 24 weeks

RESULTS

This review includes double-blind, prospective, and exploratory open label studies analyzed with intention to treat with study participants being diagnosed with HE based on clinical criteria. In the Bissonnette and Ruzicka studies, participants receiving Alitretinoin received 30 mg or 10 mg tablets by mouth while participants in the Bollag study received 20-40 mg soft gelatin capsules of Alitretinoin by mouth.^{1-2,5} The Ruzicka study had the most participants with 409, 418, and 205 participants assigned to the 30 mg, 10 mg, and placebo groups respectively. 276 participants left the study due to insufficient response or adverse effects. Therefore, 759 participants finished the study with 303 in the 30 mg group, 319 in the 10 mg group, and 137 in the placebo group.² The Bissonnette study had the next greatest number of participants with 49, 21, and 47 in the 30 mg, 10 mg, and placebo groups respectively. 24 participants were withdrawn due to adverse effects.¹ The Bollag study had the least number of total participants with 38 entering and 38 completing the study.⁵

In the studies by Ruzicka and Bissonnette, participants were evaluated with mTLSS and PGA scores at baseline. Participants were reevaluated at 12 and 24 weeks. Assessment was carried out based on severity symptoms of each case of HE. Symptoms tested consisted of erythema, scaling, lichenification/hyperkeratosis, vesiculation, edema, fissures, and pruritus/pain. Each symptom was rated on a scale from 0(absent symptoms) to 3(severe symptoms) with 21 being the maximum number of points possible.¹⁻² The Bollag study evaluated symptoms of erythema, papules/vesicles, desquamation, hyperkeratosis, rhagades, and pruritus/pain. Symptoms were recorded as rTLSS on a scale from 0(absent symptoms) to 4(severe symptoms) for a maximum score of 24.⁵ The TLSS was converted to a percentage of participants who had improvement of symptoms (reduction in TLSS scores) from baseline scores for oral Alitretinoin

groups vs. placebo as shown in Table 2.

Table 2. Median Percent Reduction in Total Lesion Symptom Score (mTLSS or rTLSS) from Baseline at each evaluation period for patients treated with oral Alitretinoin vs. Placebo for Symptoms of Hand Eczema			
Study	Therapy	Time	
		12 weeks	24 weeks
Ruzicka	30 mg oral Alitretinoin	*	75.0
	10 mg oral Alitretinoin	*	56.0
	Placebo	*	39.0
Bissonnette	30 mg oral Alitretinoin	81.3	92.4
	10 mg oral Alitretinoin	53.9	70.9
	Placebo	33.4	42.9
		16 weeks	
Bollag	20 or 40 mg oral Alitretinoin**	86.0	

*mTLSS scores not reported. If, at 12 weeks, participant had a mTLSS resulting in a PGA of “clear” or “almost clear,” treatment was discontinued. Remaining participants were evaluated at 24 weeks.²

**27 participants received 40 mg for entire treatment period; 3 participants took 40 mg for 1 month and then 20 mg for the remainder of the study due to adverse effects; 8 participants began on 20 mg, 5 of whom continued this dose while 3 had dose increased to 40 mg after 1 month due to minimal response.⁵

As shown in Table 2, percentage reduction of symptoms from baseline to the end of the studies proved to be substantial over all groups. In the Ruzicka and Bissonnette studies, participants treated with 30 mg oral Alitretinoin showed both early and clinically significant responses to treatment as compared to the 10 mg and placebo groups. The slightly decreased percentage of the TLSS in the 10 mg oral Alitretinoin group shows that treatment success is greater at higher doses. Additionally, both of these studies showed statistically significant decreases in TLSS among groups treated with 30 mg oral Alitretinoin with p -values of $p < 0.001$.¹⁻² P -values were not reported for the Bollag study though the majority of participants (86%) had very successful responses to treatment.⁵

In order to analyze results, studies with “continuous” data were converted to “dichotomous” data. This was the case for the Bollag study. It was decided that participants with “Good” to “Very Good” improvement of symptoms would be considered significant change and that participants with “None, Slight, or Moderate” improvement would be considered

insignificant change. In this way, the “experimental event rate” (EER) was determined as the percentage of participants who experienced “Good” or “Very Good “ improvement with 9-*cis*-retinoic acid (RA). The “control event rate” (CER) was determined to be the percentage of “Good or “Very Good” improvement with retinoids other than 9-*cis*-RA. As for the studies by Ruzicka and Bissonnette, data was dichotomous already and therefore required no conversion.¹⁻² Using these numbers, a Relative Benefit Increase (RBI) and an Absolute Benefit Increase (ABI) could be calculated. The Numbers Needed to Treat (NNT) of patients who needed to use Alitretinoin to improve their HE was determined from the ABI by subtracting the CER from the EER, and using the inverse result of 1/ABI. The calculated analysis of outcomes and NNT in order to decrease the severity score of patients treated with oral Alitretinoin vs. placebo for HE can be seen in Table 3.

Table 3. Analysis of Outcomes and NNT in Order to Decrease the Severity Score of Patients Treated with Alitretinoin for HE							
Study	# completed study	CER(%)	EER(%)	RBI(%)	ABI(%)	NNT(%)	<i>p</i> value
Ruzicka	759	17	48	182	31	4	<0.001
Bissonnette	93						
30 mg dose		8	80	900	72	2	<0.001
10 mg dose		10	48	380	38	3	<0.004
Bollag	38	5	89	1680	84	2	N/A

As can be seen in Table 3, the RBI was substantial in all three studies with the Bollag study showing, by far, the highest percent increase. Despite the relatively large differences in RBI among the three studies, the NNT were quite similar, ranging from 2-4 patients.

In each of the studies, participants complained of a few adverse effects to treatment, likely associated with hypervitaminosis A syndrome. The symptoms associated with this syndrome are headache, flush, conjunctivitis, mucocutaneous manifestations (chilitis, dry skin, dry lips), and musculoskeletal symptoms. Adverse effects were found to be dose dependent.^{1-2,5}

In the Ruzicka study, 276 participants left the study due to insufficient response or adverse effects while the Bissonnette study had 24 withdraw due to adverse effects.¹⁻² All participants that began the Bollag study completed it by decreasing Alitretinoin dose if patients experienced adverse effects or increasing the dose if patient showed signs of insufficient response.⁵

DISCUSSION

The Randomized Controlled Trials and Open-Label Case Series in this review of the safety and efficacy of oral Alitretinoin in the treatment of HE showed that the medication can safely and effectively treat symptoms of the condition when given at maximal tolerated doses without causing adverse effects (30-40 mg). Perhaps the Bollag study was most successful with highest RBI and lowest NNT because the study design allowed augmentation of the Alitretinoin depending on an individual's response to a particular dose. In this way, though doses varied, all participants were able to be treated until a successful outcome was reached.

Alitretinoin gel (Panretin®) was initially approved in the U.S. as topical treatment for AIDS-related Kaposi's Sarcoma. A current off-label use is for treatment of T-cell lymphoma. It was not until August 2008 that Swiss manufacturer Basilea Pharmaceutica got approval to use their product Toctino®, an oral Alitretinoin, for treatment of HE. Since then, it has been approved in other countries, including U.S., for HE treatment. However, in 2010, the National Institute for Health and Clinical Excellence (NICE) made a recommendation that Toctino® be started only in patients severely affected by HE, and be discontinued as soon as adequate response is observed, or if HE remains severe for 12 weeks, or if inadequate response at 24 weeks. Effects of long-term use are unknown.⁶

The studies evaluated by this paper were limited by the novelty of Alitretinoin as a treatment for HE. Though it has approved uses for other medical conditions, Alitretinoin is a

fairly new drug overall. Literature on oral Alitretinoin is scarce. To date, no research about oral Alitretinoin has been published in U.S. Current publications are essentially pilot studies and are broadly directed. As more is learned about the drug and its long-term effects, studies will be able to be more specifically structured.

CONCLUSION

Alitretinoin is an effective treatment for HE when the condition is refractory or unresponsive to corticosteroid therapy. The studies presented here show no severe adverse effects with use of Alitretinoin for up to a year, however, based on the most current literature and NIH recommendation, it is suspected that Alitretinoin may not be safe to use as long-term treatment for HE. Until the safety and efficacy of oral Alitretinoin can be definitively determined in a long-term trial, future research could be directed at determining more specifically the triggering agents that exacerbate HE. In this way, individuals who suffer from HE could be treated in a more preventative manner. Avoiding triggers would likely prove to be safe practice and may very well be more effective than use of a long-term topical agent. If future studies prove to be as successful as those already completed, researchers will likely continue to get the funding they need to further explore this drug which holds much promise for the many sufferers of this physically painful, emotionally frustrating, and economically consuming chronic condition.

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