

## New and Existing Therapeutic Options for Hand Eczema

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### ABSTRACT

*Hand eczema affects up to 10% of the population and encompasses a diverse range of morphological presentations and underlying pathophysiological processes. This article will review the new and existing treatments that are available for this common dermatologic problem.*

**Keywords:** botulinum toxin; calcineurin inhibitors; corticosteroids; hand eczema; immunomodulators; iontophoresis; phototherapy; retinoids; systemic immunosuppressive therapy

There is not, as yet, a standardized system for the classification of hand eczema. Warshaw et al., however, outlined a comprehensive clinical classification of hand eczema based on an extensive literature review, as well as from personal experience.<sup>1</sup> Clinical manifestations of the disorder include erythema, edema, scaling, hyperkeratosis, vesiculation, fissuring, papules, and plaques. Morphological subtypes and patterns of distribution may suggest causation, but these are not reliable predictors and etiology is usually multifactorial.<sup>2,3</sup> Atopic skin diathesis is believed to play a role in hand eczema in up to 50% of cases.<sup>4</sup> The 2 other most important causative factors are contact allergy and irritant exposure. Additional contributory factors include friction, occupation, low humidity, psychological stress, low socioeconomic status, and hyperhidrosis.<sup>5,6</sup> A specific etiology cannot be identified in some patients with hand eczema.<sup>5</sup>

Hand eczema often runs a chronic, relapsing, and remitting course despite appropriate preventative measures and treatment.<sup>5,7,8</sup> Several studies have demonstrated the psychosocial burden of chronic hand eczema on patients' lives, as well as its burden on society.<sup>9-11</sup> Despite the enormity of the problem, few well-designed, randomized controlled trials evaluating therapies have been carried out. In all hand eczema trials since 1977,<sup>3</sup> only 2,142 patients have been enrolled, and a recent European survey conducted on hand eczema identified only 31 randomized controlled trials involving a total of 1,200 participants.<sup>12</sup> The paucity of evidence-based data on therapeutic options for hand eczema has left clinicians with no clear direction for treating those patients who do not respond to conventional therapy.

### Management - Preventative Measures

The regular use of hand emollients and avoidance of frequent contact with irritants such as water, soap and detergents are the mainstays of therapy. Rubber gloves can exacerbate hand eczema, which can usually be avoided by wearing cotton liners. Contact allergy is responsible for hand eczema in as many as 47% of cases and all patients should be considered for patch testing to identify relevant allergens.<sup>13</sup> A recent study demonstrated the persistence of contact sensitivity in up to 74% of hand eczema patients who were followed for 8 years,<sup>14</sup> emphasizing the importance of continued allergen avoidance over time. Common contact allergens that can cause hand dermatitis include nickel, potassium dichromate, rubber chemicals, and biocides.

### Topical Treatments

#### Corticosteroids

Considered as the first-line therapy in the treatment of hand eczema, several trials have evaluated the efficacy of mild, moderate, or potent topical corticosteroids for hand eczema.<sup>15-17</sup> However, there are no standard recommendations about how these agents should be used. Generally, the choice of steroid potency is influenced by factors such as eczema severity, morphology, and the area involved. Drug delivery is enhanced with an ointment vehicle, as well as occlusion. In addition, water soaks for 20 minutes prior to steroid application appears to give superior results.<sup>18</sup> Agents such as salicylic acid, tar derivatives, and anthralin are adjunctive therapies and are especially useful for hyperkeratotic eczema.

It is important to keep in mind that topical corticosteroids may also be allergens. Consequently, the possibility of a

corticosteroid allergy should always be considered before attributing treatment failure to the disease itself.

### Immunomodulators

The effectiveness of topical calcineurin inhibitors in the treatment of atopic dermatitis has been well established; however, their therapeutic role in hand eczema has not been studied in randomized, double-blind, controlled trials.

In a prospective, open, multicenter study of 29 patients with occupational hand eczema, tacrolimus 0.1% (Protopic®, Astellas Pharma) was applied twice daily for 4 weeks, followed by a 2 month optional treatment period, which resulted in complete clearance in 44% of subjects.<sup>19</sup> At least a 50% improvement was achieved in 52% of patients. While only 59% of the patients continued medication usage during the optional treatment period, all subjects continued to improve during this time.

Topical tacrolimus was shown to be as effective as mometasone furoate 0.1% ointment in the treatment of dyshidrotic palmar eczema.<sup>20</sup> After a 2 week washout period, 16 patients were randomized to apply 1 of the 2 study drugs to either a palm or sole twice daily for 4 weeks. There was a comparable reduction in dyshidrotic area and severity index (DASI) scores for both study drugs when used to treat palmar eczema. However, mometasone furoate was superior to tacrolimus in the treatment of plantar eczema. For time to relapse after the active treatment phase, no difference was noted between the 2 agents.

In a multicenter, randomized, vehicle controlled trial, the effectiveness of 1% pimecrolimus cream (Elidel®, Novartis) compared with vehicle was evaluated for the treatment of chronic hand dermatitis.<sup>21</sup> Two hundred and ninety-four patients with chronic hand dermatitis of varied and mixed types were randomized to receive either vehicle or 1% pimecrolimus cream twice daily using occlusion at night. At the conclusion of the trial, on day 22, there was a trend toward greater clearance in the pimecrolimus group. Almost 28% of pimecrolimus-treated patients vs. 18% of vehicle-treated patients were clear or almost clear at the end of the study. Irritant contact dermatitis and dorsal hand involvement showed the most favorable response.

In an open-label, uncontrolled study, pimecrolimus 1% cream, applied twice daily with occlusion at night, showed favorable response for hand eczema in 85% of patients (n=12) at 3 weeks. The drug was well tolerated and measurement of pimecrolimus blood levels indicated low systemic exposure.<sup>22</sup>

Given the chronic nature of hand eczema, topical calcineurin inhibitors may provide the greatest benefit as a maintenance therapy between flares, which is akin to that adopted for the treatment of atopic dermatitis. Based on the information derived from a small number of studies, their use appears to be limited to treatment of non-hyperkeratotic hand eczema.<sup>20-22</sup>

### Retinoids

Bexarotene (Targretin®, Eisai) is a new synthetic retinoid which, in both topical and systemic forms, has been studied in the treatment of cutaneous T-cell lymphoma. In a phase 1-2 trial, 1% bexarotene gel was evaluated for safety, tolerability, and efficacy in the treatment of severe chronic hand dermatitis.<sup>23</sup> Fifty-five patients were randomized to receive treatment with either bexarotene gel alone or in combination with topical 0.1% mometasone furoate ointment or with 1% hydrocortisone ointment. Bexarotene was initially applied every other day and increased in a stepwise approach to 3 times daily as tolerated. Topical steroids were applied twice daily. Patients were evaluated regularly during the 22 week treatment period and then 4 weeks post treatment. Forty-two of 55 patients completed the study with 36% of all patients showing more than 90% clearance, and 71% showing at least a 50% improvement. The response rates in the 3 treatment groups were not statistically different. The drug was well tolerated by most patients; however, there was a 30% incidence of irritation in all treatment arms.

### Phototherapy

Phototherapy is one of the most effective treatments for hand eczema.

#### Ultraviolet B (UVB)

Narrow band UVB therapy has shown clinical efficacy in the treatment of psoriasis and atopic dermatitis.<sup>24</sup> However, there is little information about its role in the management of hand eczema.

The safety and efficacy of narrow band UVB therapy for the treatment of chronic hand eczema (dry and dyshidrotic types) was evaluated in a randomized, controlled, prospective study of 15 patients who had failed conventional topical therapy.<sup>25</sup> Patients were treated with narrow band UVB (NB-UVB) on 1 hand and topical photochemotherapy using 0.1% 8-methoxypsoralen (8-MOP) gel on the other 3 times weekly for 9 weeks. Patients were assessed every 3 weeks during the treatment period and then evaluated 10 weeks following the last treatment. All of the 12 subjects who completed the trial showed improvement noting no statistical difference between modalities.

Both broad band and narrow band UVB appear to be as effective as topical/bath psoralen + UVA (PUVA) therapy in the treatment of chronic hand dermatitis.<sup>26</sup> However, the risks of phototoxicity and dyspigmentation associated with local PUVA therapy make UVB therapy a preferable initial therapeutic option.

#### PUVA

Several studies have reported benefits from both topical and systemic PUVA therapy for chronic hand dermatitis.<sup>27-29</sup> PUVA may be the phototherapy of choice for hyperkeratotic

hand eczema given the ability for the UVA's longer wave lengths to penetrate deeper into the skin.

There appears to be little difference in efficacy between topical and systemic PUVA. In a retrospective study on localized topical and systemic photochemotherapy for chronic hand and foot dermatoses, Hawk and Grice<sup>30</sup> noted no difference in efficacy between these modalities in their treatment of 40 patients. However, the study population was mixed, with some patients having chronic eczema, while others had palmo-plantar pustulosis and psoriasis. A more recent open-label, randomized, controlled trial compared the efficacy of home administered oral PUVA with hospital delivered bath PUVA for chronic hand dermatitis in 150 patients.<sup>29</sup> The investigators found no difference between treatment groups at the end of 10 weeks of treatment and at follow-up 8 weeks later.

### **UVA-1**

UVA-1 therapy has been established as an effective treatment of atopic dermatitis in several clinical trials.<sup>31,32</sup> UVA-1 was first reported to be beneficial for dyshidrotic hand eczema in an uncontrolled trial of 12 patients.<sup>33</sup> Subjects received daily treatment with local UVA-1 irradiation at a dose of 40 J/cm<sup>2</sup> for 3 weeks. Eczema severity was evaluated using the DASI. Conditions for 10 out of 12 patients were judged to be cleared or almost cleared at the end of the treatment course and patients remained relapse free during a 3 month follow-up period. In a randomized, double-blind, placebo controlled trial, 28 patients with chronic dyshidrotic hand eczema were randomized to receive UVA-1 irradiation or placebo 5 times/week for 3 weeks. Change in DASI was the primary endpoint and patients were assessed weekly during the treatment phase and then at 3 and 6 weeks post treatment. Therapeutic response was noted in the treatment group at 2 weeks and a significant sustained reduction in DASI persisted at 6 weeks following the last treatment.

### ***Ionizing Radiation***

The inflammatory cells operative in eczema are highly radiosensitive.<sup>34</sup> Grenz rays and superficial radiotherapy were popular treatments for chronic severe hand eczema 20-30 years ago. However, their association with a greater risk for carcinogenesis coupled with the introduction of megavoltage external beam photon and electron units, has resulted in these treatments falling out of favor. Superficial radiation therapy appears to provide greater benefit than Grenz ray therapy and this is likely because of its deeper penetration into the skin. As a result of non-standardized treatment protocols, it is difficult to critically compare studies and reach valid conclusions about these forms of treatment.<sup>35-39</sup>

In a recent case report, low dose external beam megavoltage therapy resulted in complete clearance and a prolonged remission of severe treatment resistant dyshidrotic hand eczema in a 41 year-old woman.<sup>40</sup> These results are

impressive and a reminder that ionizing radiation, an often forgotten intervention for this disease, may be helpful for refractory cases.

## ***Systemic Treatments***

### **Immunosuppressive Therapy**

Systemic immunosuppressive therapy may be considered for those cases of hand eczema that are refractory to topical steroids and phototherapy. Systemic glucocorticoids are generally effective in managing acute flares; however, given their side-effect profile, they are not practical over the long-term. Similarly, the usefulness of cyclosporine for this condition seems limited to the short-term. While 1 study demonstrated prolonged disease remission in 74% of patients 1 year after a 6-week course of cyclosporine 3mg/kg/day,<sup>41</sup> other studies have shown high relapse rates within weeks of drug discontinuation.<sup>42,43</sup>

Agents such as methotrexate and mycophenolate mofetil (CellCept®, Roche Laboratories) may be more promising for long-term control of severe hand eczema. Methotrexate has been shown to be an effective adjunctive agent in 5 patients with severe recalcitrant dyshidrotic eczema. Patients were treated with methotrexate 15-22.5mg/week and all were subsequently able to significantly reduce or eliminate systemic steroid use.<sup>44</sup> In a case report of a 39 year-old male with severe dyshidrotic eczema, long-term control was ultimately achieved and maintained with mycophenolate mofetil 2-3gm/day. The drug was well tolerated without serious adverse effects after 1 year of treatment.<sup>45</sup>

### **Retinoids**

Systemic retinoids, including etretinate (Tigason®, Hoffmann-La Roche) and acitretin (Soriatane®, Stiefel), have shown some benefit in the treatment of hand eczema.<sup>34,46</sup> Studies in the past have focused on their treatment of hyperkeratotic eczema.

Alitretinoin (9-cis-retinoic acid) (Toctino®, Basilea Pharmaceuticals) is an oral retinoid that is capable of activating all retinoic acid receptors as well as retinoid X receptors. It is currently approved in Europe for the treatment of solid malignant tumors and as a new once-daily treatment for adults with severe chronic hand eczema unresponsive to potent topical corticosteroids. While it is not approved in North America, this agent, like its related compounds, has been evaluated for the treatment of chronic hand dermatitis.<sup>47</sup> In a multicenter, randomized, double-blind, placebo controlled trial, 319 patients were allocated to receive either placebo or alitretinoin at 10mg/day, 20mg/day, or 40mg/day for 12 weeks. All types of hand dermatitis were included in the study, but the majority of patients had the hyperkeratotic type. Patients were deemed to be responders if, by physician's global assessment, the dermatitis was clear or almost clear at the end of the treatment period. Of the 244 patients who completed the 12 week course, 127 were responders. Response rates increased across the dosage



range and were 27% for the placebo group and 39%, 41% and 53% for the 10, 20 and 40mg/day groups, respectively. This incremental response rate was independent of the type of hand eczema. The drug was generally well tolerated and adverse events, such as headache, mucocutaneous dryness, photosensitivity, and dyslipidemia occurred more frequently with higher drug doses.

### Botulinum Toxin

Hyperhidrosis has been reported to be an aggravating factor in dyshidrotic hand eczema in nearly 40% of cases.<sup>48</sup> As such, botulinum toxin - type A (BTX-A), which is an approved treatment for axillary hyperhidrosis and an effective, commonly used treatment of palmar hyperhidrosis, has been explored as an off-label treatment for dyshidrotic eczema.<sup>49</sup> In an open study of 10 patients with dyshidrotic hand eczema treated with 162 units of intradermal BTX-A in 1 hand only, 7 of 10 patients experienced good or very good improvement in their eczema on the treated hand at 6 weeks.<sup>50</sup> Sweating was more likely to be an aggravating factor to the eczema in responders to this formulation.

BTX-A was found to be a very effective adjuvant treatment for dyshidrotic eczema in 6 patients, who were treated with topical steroids alone on 1 hand, and a topical steroid plus 100 units of intracutaneous BTX-A at week 0 in the other, more severely affected hand. There was a significantly greater drop in DASI scores in the combination treatment side with a stabilization of hand eczema at 8 weeks, whereas there was a 50% partial or complete relapse rate on the monotherapy side. Pruritus and vesiculation decreased more rapidly in the combination therapy side. The authors concluded that BTX-A inhibition of substance P release may be operative in these antipruritic effects.<sup>51</sup>

### Iontophoresis

Hyperhidrosis, a recognized risk factor for hand eczema, generally responds well to treatment with tap water iontophoresis.<sup>52</sup> In a randomized half-side study of 20 patients with mild-to-moderate dyshidrotic eczema, patients received steroid free topical therapy of both hands and daily unilateral tap water iontophoresis. Significant improvement in eczema, as assessed by DASI scores, was noted only in iontophoresis treated hands. The authors attributed improvement to a reduction in sweat secretion and possibly enhanced absorption of topical therapy.<sup>53</sup>

### Conclusion

Hand eczema is a highly prevalent disorder, which in many patients is chronic, debilitating, and associated with impaired quality of life. Both endogenous and exogenous factors play a role in the development of the disease. Lifestyle management, the use of emollients, avoidance of allergens, and topical corticosteroids are effective and sufficient treatments for some patients, but many require additional intervention. The best way to manage these patients is unclear based on the current level of evidence. A

standardized, universally accepted classification system of hand eczema and larger scale, well-designed, randomized trials are necessary prerequisites to achieve optimal and successful management of this disorder.

### References

1. Warshaw E, Lee G, Storrs FJ. Hand dermatitis: a review of clinical features, therapeutic options, and long-term outcomes. *Am J Contact Dermat* 14(3):119-37 (2003 Sep).
2. Magina S, Barros MA, Ferreira JA, et al. Atopy, nickel sensitivity, occupation, and clinical patterns in different types of hand dermatitis. *Am J Contact Dermat* 14(2):63-8 (2003 Jun).
3. Diepgen TL, Agner T, Aberer W, et al. Management of chronic hand eczema. *Contact Dermatitis* 57(4):203-10 (2007 Oct).
4. Coenraads PJ, Diepgen TL. Risk of hand eczema in employees with past or present atopic dermatitis. *Int Arch Occup Environ Health* 71(1):7-13 (1998 Feb).
5. Veien NK, Hattel T, Laurberg G. Hand eczema: causes, course, and prognosis I. *Contact Dermatitis* 58(6):330-4 (2008 Jun).
6. Lerbaek A, Kyvik KO, Ravn H, et al. Clinical characteristics and consequences of hand eczema – an 8-year follow-up study of a population-based twin cohort. *Contact Dermatitis* 58(4):210-6 (2008 Apr).
7. Veien NK, Hattel T, Laurberg G. Hand eczema: causes, course, and prognosis II. *Contact Dermatitis* 58(6):335-9 (2008 Jun).
8. Meding B, Wrangsjö K, Järholm B. Fifteen-year follow-up of hand eczema: persistence and consequences. *Br J Dermatol* 152(5):975-98 (2005 May).
9. Niemeier V, Nippesen M, Kupfer J, et al. Psychological factors associated with hand dermatoses: which subgroup needs additional psychological care? *Br J Dermatol* 146(6):1031-7 (2002 Jun).
10. Cvetkovski RS, Zachariae R, Jensen H, et al. Quality of life and depression in a population of occupational hand eczema patients. *Contact Dermatitis* 54(2):106-11 (2006 Feb).
11. Agner T, Andersen KE, Brandao FM, et al. Hand eczema severity and quality of life: a cross-sectional, multicentre study of hand eczema patients. *Contact Dermatitis* 59(1):43-7 (2008 Jul).
12. Van Coevorden AM, Coenraads PJ, Svensson A, et al. Overview of studies of treatment for hand eczema – the EDEN hand eczema survey. *Br J Dermatol* 151(2):446-51 (2004 Aug).
13. Li WF, Wang J. Contact hypersensitivity in hand dermatitis. *Contact Dermatitis* 47(4):206-9 (2002 Oct).
14. Lerbaek A, Kyvik KO, Menné T, et al. Retesting with the TRUE Test in a population-based twin cohort with hand eczema – allergies and persistence in an 8-year follow-up study. *Contact Dermatitis* 57(4):248-52 (2007 Oct).
15. Veien NK, Olholm Larsen P, Thestrup-Pedersen K, et al. Long-term, intermittent treatment of chronic hand eczema with mometasone furoate. *Br J Dermatol* 140(5):882-6 (1999 May).
16. Uggeldahl PE, Kero M, Ulshagen K, et al. Comparative effects of desonide cream 0.1% and 0.05% in patients with hand eczema. *Curr Ther Res* 40:969-73 (1986).
17. Gupta AK, Shear NH, Lester RS, et al. Betamethasone dipropionate polyacrylic film-forming lotion in the treatment of hand dermatitis. *Int J Dermatol* 32(11):828-9 (1993 Nov).
18. Gutman AB, Kligman AM, Sciacca J, et al. Soak and Smear: a standard technique revisited. *Arch Dermatol* 141(12):1556-9 (2005 Dec).
19. Schliemann S, Kelterer D, Bauer A, et al. Tacrolimus ointment in the treatment of occupationally induced chronic hand dermatitis. *Contact Dermatitis* 58(5):299-306 (2008 May).

20. Schnopp C, Remling R, Möhrenschrager M, et al. Topical tacrolimus (FK506) and mometasone furoate in treatment of dyshidrotic palmar eczema: a randomized, observer-blinded trial. *J Am Acad Dermatol* 46(1):73-7 (2002 Jan).
21. Belsito DV, Fowler JF Jr, Marks JG Jr, et al. Pimecrolimus cream 1%: a potential new treatment for chronic hand dermatitis. *Cutis* 73(1):31-8 (2004 Jan).
22. Thaci D, Steinmeyer K, Ebelin ME, et al. Occlusive treatment of chronic hand dermatitis with pimecrolimus cream 1% results in low systemic exposure, is well tolerated, safe, and effective. An open study. *Dermatology* 207(1):37-42 (2003).
23. Hanifin JM, Stevens V, Sheth P, et al. Novel treatment of chronic severe hand dermatitis with bexarotene gel. *Br J Dermatol* 150(3):545-53 (2004 Mar).
24. Ibbotson SH, Bilsland D, Cox NH, et al. An update and guidance on narrowband ultraviolet B phototherapy: a British photodermatology group workshop report. *Br J Dermatol* 151(2):283-97 (2004 Aug).
25. Sezer E, Etikan I. Local narrowband UVB phototherapy vs. local PUVA in the treatment of chronic hand eczema. *Photodermatol Photoimmunol Photomed* 23(1):10-4 (2007 Feb).
26. Simons JR, Bohnen IJ, van der Valk PG. A left-right comparison of UVB phototherapy and topical photochemotherapy in bilateral chronic hand dermatitis after 6 weeks' treatment. *Clin Exp Dermatol* 22(1):7-10 (1997 Jan).
27. Schempp CM, Müller H, Czech W, et al. Treatment of chronic palmoplantar eczema with local bath-PUVA therapy. *J Am Acad Dermatol* 36(5 Pt 1):733-7 (1997 May).
28. Morison WL, Parrish JA, Fitzpatrick TB. Oral methoxsalen photochemotherapy of recalcitrant dermatoses of the palms and soles. *Br J Dermatol* 99(3):293-302 (1978 Sep).
29. van Coevorden AM, Kamphof WG, van Sonderen E, et al. Comparison of oral psoralen-UV-A with a portable tanning unit at home vs hospital-administered bath psoralen-UV-A in patients with chronic hand eczema: an open-label randomized controlled trial of efficacy. *Arch Dermatol* 140(12):1463-6 (2004 Dec).
30. Hawk JL, Grice PL. The Efficacy of localized PUVA therapy for chronic hand and foot dermatoses. *Clin Exp Dermatol* 19(6):479-82 (1994 Nov).
31. Abeck D, Schmidt T, Fesq H, et al. Long-term efficacy of medium-dose UVA1 phototherapy in atopic dermatitis. *J Am Acad Dermatol* 42(2 Pt 1):254-7 (2000 Feb).
32. Krutmann J, Czech W, Diepgen T, et al. High-dose UVA1 therapy in the treatment of patients with atopic dermatitis. *J Am Acad Dermatol* 26(2 Pt 1):225-30 (1992 Feb).
33. Schmidt T, Abeck D, Boeck K, et al. UVA-1 Irradiation is effective in treatment of chronic vesicular dyshidrotic hand eczema. *Acta Derm Venereol* 78(4):318-9 (1998 Jul).
34. Thestrup-Pedersen K, Andersen KE, Menné T, et al. Treatment of hyperkeratotic dermatitis of the palms (eczema keratoticum) with oral acitretin: a single-blind placebo-controlled study. *Acta Derm Venereol* 81(5):353-5 (2001 Oct-Nov).
35. Cartwright PH, Rowell NR. Comparison of Grenz rays versus placebo in the treatment of chronic hand eczema. *Br J Dermatol* 117(1):73-6 (1987 Jul).
36. Lindelöf B, Wrangsjö K, Lidén S. A double-blind study of Grenz ray therapy in chronic eczema of the hands. *Br J Dermatol* 117(1):77-80 (1987 Jul).
37. Fairris GM, Jones DH, Mack DP, et al. Conventional superficial X-ray versus Grenz ray therapy in the treatment of constitutional eczema of the hands. *Br J Dermatol* 112(3):339-41 (1985 Mar).
38. Fairris GM, Mack DP, Rowell NR. Superficial X-ray therapy in the treatment of constitutional eczema of the hands. *Br J Dermatol* 111(4):445-9 (1984 Oct).
39. King CM, Chalmers RJ. A double-blind study of superficial radiotherapy in chronic palmar eczema. *Br J Dermatol* 111(4):451-4 (1984 Oct).
40. Stambaugh MD, DeNittis AS, Wallner PE, et al. Complete remission of refractory dyshidrotic eczema with the use of radiation therapy. *Cutis* 65(4): 211-4 (2000 Apr).
41. Granlund H, Erkkö P, Reitamo S. Long-term follow-up of eczema patients treated with cyclosporine. *Acta Derm Venereol* (Stockh) 78(1):40-3 (1998 Jan).
42. Granlund H, Erkkö P, Eriksson E, et al. Comparison of cyclosporine and topical betamethasone-17, 21-dipropionate in the treatment of severe chronic hand eczema. *Acta Derm Venereol* 76(5):371-6 (1996 Sep).
43. Petersen CS, Menné T. Cyclosporine A responsive chronic severe vesicular hand eczema. *Acta Derm Venereol* 72(6):436-7 (1992 Nov).
44. Egan CA, Rallis TM, Meadows KP, et al. Low-dose oral methotrexate treatment for recalcitrant palmoplantar pompholyx. *J Am Acad Dermatol* 40(4):612-4 (1999 Apr).
45. Pickenäcker A, Luger TA, Schwartz T. Dyshidrotic eczema treated with mycophenolate mofetil. *Arch Dermatol* 134(3): 378-9 (1998 Mar).
46. Deschamps P, Leroy D, Pedailles S, et al. Keratoderma climactericum (Haxthausen's disease): clinical signs, laboratory findings and etretinate treatment in 10 patients. *Dermatologica* 172(5):258-62 (1986).
47. Bollag W, Ott F. Successful treatment of chronic hand eczema with oral 9-cis-retinoic acid. *Dermatology* 199(4):308-12 (1999).
48. Lodi A, Betti R, Chiarelli G, et al. Epidemiological, clinical and allergological observations on pompholyx. *Contact Dermatitis* 26(1):17-21 (1992 Jan).
49. Solish N, Bertucci V, Dansereau A, et al. A comprehensive approach to the recognition, diagnosis and severity-based treatment of focal hyperhidrosis. Recommendations of the Canadian Hyperhidrosis Advisory Committee. *Dermatol Surg* 33(8):908-23 (Aug 2007).
50. Swartling C, Naver H, Lindberg M, et al. Treatment of dyshidrotic hand dermatitis with intradermal botulinum toxin. *J Am Acad Dermatol* 47(5):667-71 (2002 Nov).
51. Wollina U, Karamfilov T. Adjuvant botulinum toxin A in dyshidrotic hand eczema: a controlled prospective pilot study with left-right comparison. *J Eur Acad Dermatol Venereol* 16(1):40-2 (2002 Jan).
52. Holzle E, Alberti N. Long-term efficacy and side effects of tap water iontophoresis of palmoplantar hyperhidrosis – the usefulness of home therapy. *Dermatologica* 175(3):126-35 (1987).
53. Odia S, Vocks E, Rakoski J, et al. Successful treatment of dyshidrotic hand eczema using tap water iontophoresis with pulsed direct current. *Acta Derm Venereol* 76(6):472-4 (1996 Nov).

# Treatments for Pityriasis Rosea

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## ABSTRACT

*Pityriasis rosea is a common skin disorder in children and young adults. It is a self-limiting disease with symptoms that are typically mild and tolerable. Consequently, the best treatment remains the one followed so far by generations of dermatologists: reassuring the patient and letting the condition go away on its own. However, there are times when treatment is recommended. In this paper, we review the available treatments for this skin disease.*

**Keywords:** erythroderma; pityriasis rosea; pruritus

Discussing the treatment of pityriasis rosea (PR) with patients can be a frustrating experience. As a self-limiting disease, the best treatment regime is to reassure the patient and let the condition resolve on its own. In our experience, pruritus, when it occurs, is always mild and tolerable. Those complaining of severe pruritus have usually been “treated” either within their family, by a pharmacist, or by an inexperienced physician. For such cases, and for those who have received corticosteroids,<sup>1</sup> the eruption may tend to turn into erythroderma.

A recent Cochrane collaboration paper reviewed the literature on the different types of treatment used.<sup>2</sup> There is inadequate evidence for the efficacy of all topical medications (i.e., emollients, antihistamines, and corticosteroids). Other agents that have not been found to be significantly active include sunlight, artificial UV therapy, systemic antihistamines and corticosteroids, antiviral agents, and intravenous glycyrrhizin. There is some evidence that oral erythromycin may shorten the course of the rash and alleviate pruritus, and a recent publication reported a 73% cure rate, although 12% of the patients experienced gastrointestinal disturbances.<sup>3</sup> In this paper we will discuss new and existing evidence that maintain some significance today.

### Antibiotics

The erythromycin issue has been raised very recently. In a placebo-controlled study of 184 patients who were comparable in sex, age, and mean duration of disease at the time they attended the clinic, adult patients were treated with 200mg of erythromycin 4 times daily and children were given 20-40mg/kg daily in 4 divided doses. Controls were given a placebo (an emollient cream) that was not identical in appearance. Subjects were seen for follow-up visits at weeks 2, 4, 6, and 8 following the start of treatment. No significant difference between the 2 treatment groups were found at weeks 4, 6, and 8.<sup>3</sup>

In a double-blind, placebo-controlled clinical study, 90 patients, who were comparable with regard to age at presentation, sex, and average duration of disease at the time of reporting to the clinic, were alternatively treated for 14 days with erythromycin in divided doses or assigned to

the placebo group. All patients were followed for 6 weeks. Complete response was observed in 33 patients (73.33%) in the treatment group and none in the placebo group.<sup>4</sup> However, it should be noted that of the studies mentioned in the Cochrane collaboration paper above,<sup>2</sup> this study was excluded because of the lack of randomization.

Clarithromycin was studied in 52 patients presenting with a PR rash of 7 days duration or less. Patients were started on oral clarithromycin 250mg twice daily for 2 weeks. In 50 patients, the lesions regressed by the end of week 1, mostly cleared by the end of week 2, and completely disappeared by the end of week 4. In 2 patients, the condition resolved after 6 weeks.<sup>5</sup>

Azithromycin was studied in 49 children in order to explore its fewer adverse effects and greater biological half-life, while still having a spectrum of antimicrobial activity. Its activity is very similar to erythromycin. Patients were randomly assigned to azithromycin (12mg/kg/day, up to a maximum of 500mg/day) for 5 days or to a similar-appearing placebo. Rates of cure and partial resolution were similar in the azithromycin and placebo groups.<sup>6</sup>

### Antivirals

Beta-guanine analogues, e.g., 9-(2-hydroxyethoxymethyl) guanine or acyclovir, have low activity on human herpesvirus-6 (HHV-6) and -7 (HHV-7). The *in vitro* median effective concentration (EC50) values of acyclovir are approximately 6-8mg/mL for HHV-6A, 16-24mg/mL for HHV-6B, and 121-128mg/mL for HHV-7. In addition, the sensitivity of HHV-7 is different from HHV-6.<sup>7</sup> Nonetheless, considering the association of PR with HHV-6 and -7,<sup>8</sup> acyclovir 400mg every 4 hours for 5 days has been tried in a single patient with almost total resolution of PR and non-recurrence of the rash in 6 days.<sup>9</sup> However, this patient had a persistent form of PR, and lesions had been exacerbated by repeated UVB exposures over 1 week. In 2006, we studied the effect of acyclovir in 87 consecutive patients who were treated for 1 week with either oral acyclovir (800mg 5 times daily) or placebo. In all patients, the time of lesion clearing and the number of new lesions appearing during treatment were recorded. On the 14th day of treatment, 79% of treated



patients fully regressed compared with 4% of patients in the placebo group. The lesions cleared in 18.5 days for treated patients and in 37.9 days for the placebo group. Clearance was achieved in 17.2 days in patients treated in the first week from onset and in 19.7 days in the patients treated later. On the 7th day, there were significantly fewer new lesions in patients treated in the first week than in those treated later. The trial, however, was neither randomized nor double-blinded. Objectivity was nonetheless achieved by counting the lesions. It is likely that the efficacy of acyclovir is high when the virus is in replication, i.e., in the first week from onset. Unfortunately, dermatologists very rarely see patients just after the onset of the disease, as the patients usually seek the specialist's advice only after trying familiar remedies.<sup>10</sup> However, 1 case has been published reporting the occurrence of PR during acyclovir treatment.<sup>11</sup>

### Phototherapy

After its introduction in 1974,<sup>12</sup> phototherapy has not acquired many supporters for treating PR. Recently, however, interest has again been raised. In a bilateral comparison study that was also excluded from the Cochrane collaboration paper because it was not randomized, Leenutaphong et al.<sup>13</sup> treated 17 patients 5 times/week with unilateral UVB phototherapy. One joule of UVA was used as a "placebo" on the untreated side. After 10 daily erythemogenic exposures of UVB, the severity decrease was greater on the affected side than on the placebo side in 15 of 17 patients. The overall reduction of the severity score was significantly different after the third treatment. However, during the follow-up period, the 2 sides were indistinguishable with regard to severity score and pruritus. The duration of disease was not related to the success of UVB phototherapy. In another study excluded by the Cochrane collaboration paper, Valkova et al. studied 101 patients of various ages and phototypes in whom PR had lasted between 7 and 25 days. The irradiation sessions were held in a conventional UV cabin (Waldmann 7001 K). One group was treated with an initial 80% minimal erythema dose that was progressively increased according to the degree of the preceding erythema. The right half of the body was irradiated with UVB, and UVA (1 J/cm<sup>2</sup>) was given as a placebo to the left half of the body. A second group was given UVB irradiation on the whole body with an initial dose determined by the patient's phototype. The procedures were held 4 times weekly. UVA irradiation had no effect on the course of the disease, but total clearing of the rash was observed after UVB phototherapy. Irritation of the rash was observed in 7% of cases. Interestingly, the duration of the disease and the duration of UVB therapy were related. The number of procedures necessary for total recovery can be calculated according to the following equation: Number of procedures =  $4.34 + [0.05 \times \text{duration of the disease (in days)}]$ .<sup>14</sup>

### Special Circumstances

There are peculiar conditions, however, in which a systemic treatment could be initiated. In children, pruritus may be

common and intense, necessitating treatment, e.g., in a recent survey in Burkina-Faso, only 55.5% of school children were left untreated.<sup>15</sup> In suberythrodermic forms, oral methylprednisolone (16mg/day) can be safely prescribed. During pregnancy, especially for widespread forms, in the absence of an antiviral drug effective on HHV-6/-7, high doses of acyclovir may prevent miscarriage or premature births.<sup>16</sup> In pregnancy, acyclovir efficacy and safety needs to be confirmed.

### Conclusion

Only rarely does PR need to be treated. Often, topical remedies induce pruritus. Systemic treatment with oral methylprednisolone can be advocated when pruritus is difficult to manage, lesions are widespread, and erythroderma may supervene. Even in such cases caution is needed, however, for the possible exacerbation of PR lesions.

### References

1. Leonforte IF. Pityriasis rosea: exacerbation with corticosteroid treatment. *Dermatologica* 163(6):480-1 (1981).
2. Chuh AA, Dofitas BL, Comisel GG, et al. Interventions for pityriasis rosea. *Cochrane Database Syst Rev* 2:CD005068 (2007).
3. Rasi A, Tajziehchi L, Savabi-Nasab S. Oral erythromycin is ineffective in the treatment of pityriasis rosea. *J Drugs Dermatol* 7(1):35-8 (2008 Jan).
4. Sharma PK, Yadav TP, Gautam RK, et al. Erythromycin in pityriasis rosea: a double-blind, placebo-controlled clinical trial. *J Am Acad Dermatol* 42(2 Pt 1):241-4 (2000 Feb).
5. Bukhari IA. Oral erythromycin is ineffective in the treatment of pityriasis rosea. *J Drugs Dermatol* 7(7):625 (2008 Jul).
6. Amer A, Fischer H. Azithromycin does not cure pityriasis rosea. *Pediatrics* 117(5):1702-5 (2006 May).
7. Yoshida M, Yamada M, Tsukazaki T, et al. Comparison of antiviral compounds against human herpesvirus 6 and 7. *Antiviral Res* 40(1-2): 73-84 (1998 Dec).
8. Broccolo F, Drago F, Careddu AM, et al. Additional evidence that pityriasis rosea is associated with reactivation of human herpesvirus-6 and -7. *J Invest Dermatol* 124(6):1234-40 (2005 Jun).
9. Castanedo-Cazares JP, Lepe V, Moncada B. Antivirals for pityriasis rosea. *Photodermatol Photoimmunol Photomed* 20(2):110 (2004 Apr).
10. Drago F, Vecchio F, Rebora A. Use of high-dose acyclovir in pityriasis rosea. *J Am Acad Dermatol* 54(1):82-5 (2006 Jan).
11. Laxman M. Pityriasis rosea occurring during acyclovir therapy. *Indian J Dermatol Venereol Leprol* 73(3):200-1 (2007 May-Jun).
12. Merchant M, Hammond R. Controlled study of ultraviolet light for pityriasis rosea. *Cutis* 14:548-9 (1974).
13. Leenutaphong V, Jiamton S. UVB phototherapy for pityriasis rosea: a bilateral comparison study. *J Am Acad Dermatol* 33(6):996-9 (1995 Dec).
14. Valkova S, Trashlieva M, Christova P. UVB phototherapy for pityriasis rosea. *J Eur Acad Dermatol Venereol* 18(1):111-2 (2004 Jan).
15. Traore A, Korsaga-Some N, Niamba P, et al. [Pityriasis rosea in secondary schools in Ouagadougou, Burkina Faso] *Ann Dermatol Venereol* 128(5):605-9 (2001 May).
16. Drago F, Broccolo F, Zaccaria E, et al. Pregnancy outcome in patients with pityriasis rosea. *J Am Acad Dermatol* 58(5 Suppl 1):S78-83 (2008 May).

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**Update on Drugs**

Name/Company	Approval Dates/Comments
<b>Ustekinumab</b> <i>Stelara</i> ® Janssen-Ortho	HPB Canada approved this new cytokine inhibitor in December 2008 for the treatment of moderate-to-severe plaque psoriasis. This biologic was also approved by the European Commission in January 2009 for the treatment of moderate-to-severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systematic therapies including cyclosporin, methotrexate and PUVA.
<b>Photopheresis System</b> <i>THERAKOS™ CELLEX™</i> Johnson & Johnson	HPB Canada approved this system in January 2009 for the palliative treatment of skin manifestations of cutaneous T-cell lymphoma that are unresponsive to other forms of treatment.
<b>Calcitriol</b> <i>Vectical™ Ointment</i> Galderma Laboratories	The US FDA approved this topical vitamin D3 agent in February 2009 for the treatment of mild-to-moderate plaque psoriasis in adults.
<b>Autologous Collagen Cellular Processing System</b> <i>Isolagen Therapy™</i> Isolagen, Inc.	The US FDA received a Biologics License Application for this novel, first-in-class cellular therapy in March 2009 for the treatment of wrinkles/nasolabial folds.

**Drug News**

Over the past 7 months, 3 virologically confirmed cases of progressive multifocal leukoencephalopathy (PML) have been reported in psoriasis patients treated with efalizumab (Raptiva®, Merck Serono/Genentech), which is currently approved in Europe, the US, and Canada for the treatment of adult patients with moderate-to-severe chronic plaque psoriasis who have failed to respond to or who have contraindication to, or are intolerant to certain other systemic therapies. As a result, in February 2009, the European Medicines Agency (EMA) recommended the suspension of the marketing authorization for this product, and after review, the EMA concluded that the benefits of efalizumab no longer outweigh its risks. Also in February 2009, Health Canada concluded that the risks outweighed the benefits of this T-cell modulator and suspended its availability in Canada. The US FDA also issued a public health advisory for this drug and is reviewing the reports. The FDA says it will take appropriate steps to ensure that the risks do not outweigh the benefits, and that patients who are prescribed this drug are clearly informed of PML's signs and symptoms. Health care professionals should carefully monitor for any signs of PML in patients who are taking efalizumab or have discontinued therapy. Physicians in these areas are advised to review the treatment of patients currently receiving this medicine and assess the most appropriate alternative.

In February 2009, the EMA reviewed the available information on cases of status epilepticus with myoclonus reported in 2 girls vaccinated with the cervical cancer vaccine Gardasil®. Based on the current data, the Agency's Committee for Medicinal Products for Human Use has concluded that the cases are unlikely to be related to the vaccination and that the benefits of this vaccine continue to outweigh its risk. Therefore, the Committee is recommending that vaccination with Gardasil® should continue in accordance with national vaccination programs in Member States.