



Pachyonychia Congenita Project

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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.

An appraisal of oral retinoids in the treatment of pachyonychia congenita

Robert Gruber, MD,^a Michael Edlinger, MSc,^b Roger L. Kaspar, PhD,^c C. David Hansen, MD,^d Sancy Leachman, MD, PhD,^d Leonard M. Milstone, MD,^c Frances J. D. Smith, PhD,^f Alexis Sidoroff, MD,^a Peter O. Fritsch, MD,^a and Matthias Schmuth, MD^a
Innsbruck, Austria; Santa Cruz, California; Salt Lake City, Utah; New Haven, Connecticut; and Dundee, United Kingdom

Background: Pachyonychia congenita (PC), a rare autosomal-dominant keratin disorder caused by mutations in keratin genes *KRT6A/B*, *KRT16*, or *KRT17*, is characterized by painful plantar keratoderma and hypertrophic nail dystrophy. Available studies assessing oral retinoid treatment for PC are limited to a few case reports.

Objective: We sought to assess overall effectiveness, adverse effects, and patient perspective in patients with PC receiving oral retinoids.

Methods: In a questionnaire-based retrospective cross-sectional survey of 30 patient with PC assessing oral retinoids (10-50 mg/d for 1-240 months), we determined the clinical score, satisfaction score, visual analog pain scale, and adverse effects.

Results: In 50% of patients there was thinning of hyperkeratoses (average improvement 1.6 on a scale from -3 to +3) (95% confidence interval 1.2-1.9, $P < .001$). In all, 14% observed amelioration of their pachyonychia; 79% did not experience any nail change. The self-reported overall satisfaction score with oral retinoid treatment was 2 or greater in 50% of the patients (mean 4.5 on a scale of 1-10). Although 33% reported decreased and 27% increased plantar pain with treatment, 40% did not notice any pain change. All patients experienced adverse effects, and 83% reported to have discontinued medication. Risk/benefit analysis favored lower retinoid doses (≤ 25 mg/d) over a longer time period (>5 months), compared with higher doses (>25 mg/d) for a shorter time (≤ 5 months).

Limitations: The retrospective, cross-sectional study design is prone to a recall bias.

Conclusion: Oral retinoids are effective in some patients with PC. However, many patients discontinued medication because adverse effects outweighed the benefits. Careful dose titration is warranted in patients informed about potential adverse effects. (J Am Acad Dermatol 10.1016/j.jaad.2011.02.003.)

Key words: keratins; keratoderma; oral retinoids; pachyonychia congenita.

Pachyonychia congenita (PC) (Online Mendelian Inheritance in Man [OMIM] #167200 for PC-1, #167210 for PC-2) is a rare autosomal-dominant ectodermal dysplasia that is characterized by hypertrophic nail dystrophy,

extremely painful diffuse or focal symmetrical hyperkeratosis of palms and soles sometimes associated with erosions, follicular keratosis on the extensor surfaces of the extremities, oral leukokeratosis, and other ectodermal defects.¹⁻³ At the molecular level,

From the Department of Dermatology^a and Department of Medical Statistics, Informatics and Health Economics,^b Innsbruck Medical University; TransDerm Inc, Santa Cruz^c; Department of Dermatology, University of Utah^d; Department of Dermatology, Yale University School of Medicine, New Haven^e; and College of Life Science, University of Dundee.^f

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Reprint requests: Matthias Schmuth, MD, Department of Dermatology, Innsbruck Medical University, Anichstr. 35, 6020 Innsbruck, Austria. E-mail: matthias.schmuth@i-med.ac.at.

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PC is caused by dominant-negative mutations in keratin genes *KRT6A*, *KRT6B*, *KRT16*, and *KRT17*.⁴⁻⁶ As these keratins are expressed in differentiated epithelial structures such as the nail bed, palmoplantar epidermis, and the oral mucosa, these are the affected tissues in PC-1.^{2,5} The hitherto common division of PC into PC-1 and PC-2 subtypes according to the clinical presentation is being increasingly replaced with genotype-inclusive nomenclature (eg, PC-K6a, PC-K6b, PC-K16, and PC-K17).⁷

Treatment of PC is notoriously difficult. Because PC is rare (~1:500,000-1:1000,000), available studies assessing therapeutic regimen are limited to a few case reports and case series. Basic measures include topical emollients, keratolytic agents, mechanical removal of excessive hyperkeratotic skin, and avoidance of physical activity. Among the systemic agents for treatment of PC, the best results have been reported with oral administration of vitamin A derivatives, ie, retinoids.⁸⁻¹¹ However, the evidence for their effectiveness is based on anecdotal reports and no systematic retrospective or prospective studies are available. For severe inherited disorders of cornification such as ichthyoses and psoriasis, oral retinoid therapy represents the treatment of choice.^{12,13} In PC, this therapeutic approach is particularly attractive, because in screening assays, retinoids have been noted to suppress mutant keratin expression (W.H. Irwin McLean, DSc, FRSE, oral communication, May 2010). We here present a questionnaire-based retrospective cross-sectional survey of 30 patients assessing effectiveness, adverse effects, and overall patient satisfaction of oral retinoid therapy for PC. Our goal was to establish the benefit/risk ratio, identify favorable dosing regimens, and determine if a future prospective trial for oral retinoid treatment of PC is justified.

METHODS

Patients

All individuals presenting with PC with known mutations in *KRT6a*, *KRT16*, or *KRT17* who were enrolled in the International Pachyonychia Congenita Research Registry between 2004 and 2010 and previously treated with oral retinoids (acitretin, etretinate, isotretinoin, or vitamin A) at different doses and durations (Table I) were

included in this questionnaire-based retrospective cross-sectional study. The study was conducted in accordance with the principles of the Declaration of Helsinki and written informed consent was obtained from all 30 patients before enrollment.

CAPSULE SUMMARY

- Available studies assessing oral retinoid treatment for pachyonychia congenita (PC), a rare keratin disorder characterized by painful plantar keratoderma and nail dystrophy, are limited to a few case reports.
- Our study shows that although treatment of PC with oral retinoids is effective in some individuals with PC, increased pain is a common adverse effect.
- The study presents the benefit/risk ratio of oral retinoids in PC and provides new insight in favorable dosing regimens.

Questionnaire

Questionnaire-based patient scoring was used to evaluate clinical score, satisfaction score, visual analog pain scale, and adverse effects of treatment with oral retinoids by self-assessment. Patients were either interviewed in person or via telephone. The questionnaire items are summarized in Table II.

Statistics

All data were analyzed with software (SPSS, Version 17.0 for Windows, SPSS Inc, Chicago, IL). Statistical differences between groups were

determined by using the Mann-Whitney U test with significance conferred when *P* less than .05. To assess predictors of the effectiveness of drug treatment we estimated odds ratios and 95% confidence intervals (CIs) with logistic regression modeling; this analysis was restricted to the retinoids acitretin and isotretinoin given the small number of cases on other retinoids.

RESULTS

Natural course of plantar hyperkeratoses in PC

As PC is a dynamic disease, 25 of the 30 patients (83%) (Table I) who received oral retinoids reported spontaneous changes in plantar hyperkeratoses while not using any medication. On a scale of -3 (much worse) to +3 (much better) plantar thickening was reported to range between -1.8 and 0.9, with an average change of -0.45, ie, the majority of patients reported worsening of the disease while not taking any drugs. These results indicate that without medication plantar hyperkeratoses in PC varies over time with little spontaneous improvement.

Treatment effectiveness

Fifteen patients (50%) reported decreased plantar hyperkeratoses, ie, thinning of calluses, when taking medication (Fig 1). On a scale from -3 (much worse) to +3 (complete improvement) the average

Table I. Patient demographics and retinoid therapy

No.	Gene	Mutation	Sex	Retinoid	Dose, mg/d	Duration, mo
1	K6a	D432_E470dup	F	Isotretinoin	NA	1
2	K16	N125D	M	Isotretinoin	25	24
3	K6a	N172del	M	Etretinate	50	6
4	K16	L132P	F	Acitretin	NA	6
5	K6a	N171K	F	Isotretinoin	NA	3
6	K17	N92S	F	Isotretinoin	50	3
7	K16	L132P	F	Etretinate	12,5	240
8	K16	L132P	F	Acitretin	50	12
9	K6a	L468P	F	Acitretin	10	24
10	K6a	L469R	F	Isotretinoin	NA	6
11	K16	L132P	M	Acitretin	NA	12
12	K6a	N171Y	M	Acitretin	25	60
13	K16	S130del	M	Isotretinoin	40	1
14	K17	N92S	F	Isotretinoin	40	6
15	K16	L132P	F	Isotretinoin	40	6
16	K6a	N172del	F	Acitretin	25	4
17	K6a	E461K	M	Isotretinoin	NA	3
18	K16	K15X	F	Isotretinoin	NA	3
19	K17	M88T	F	Isotretinoin	40	9
20	K17	M88T	M	Acitretin	25	24
21	K17	N92S	M	Isotretinoin	NA	3
22	K16	L124H	F	Acitretin	30	3
23	K16	N125S	M	Acitretin	25	3
24	K6a	L468P	F	Isotretinoin	40	6
25	K17	N92S	F	Isotretinoin	NA	2
26	K16	L132P	M	Acitretin	25	5
27	K16	N125S	M	Acitretin	20	4
28	K6a	N172del	M	Etretinate	10	2
29	K6a	N172del	M	Acitretin	25	12
30	K16	L132P	F	Ro-A-Vit	50	1

F, Female; M, male; NA, not applicable.

improvement was 1.6 (95% CI 1.2-1.9, $P < .001$). Although 4 of the 28 patients (14%) for whom data on nail thickening were available reported amelioration of their pachyonychia (thinning of nails, lighter color) with an average improvement of 1.5 on a scale from -3 to $+3$, the majority of the individuals, ie, 22 (79%), did not experience any change in nail involvement and only two patients (7%) reported worsening of their pachyonychia. The self-reported overall satisfaction score with oral retinoid treatment was greater than or equal to 2 in 15 patients (50%), with a mean of 4.5 on a scale of 1 (lowest) to 10 (highest). Notably, only 7 patients (23%) recommend the use of oral retinoids to others and even fewer, 5 patients (17%), are still using the medication.

Effects on pain

Before treatment with oral retinoids, the overall pain when walking was quantified by a visual analog pain scale (0 meaning no pain and 10 the worst pain ever experienced) and reported as 6, which signified

dreadful pain. Decreased plantar pain during therapy was reported in 10 patients (33%) whereas 8 patients (27%) experienced increased pain and the remaining 12 patients (40%) did not report any change in their pain.

In the majority of individuals with decreased pain, the improvement occurred within the first 3 to 4 weeks of taking oral retinoids. In the 10 patients with decreased plantar pain, the degree of pain amelioration ranged from 1 to 7 on a scale of 1 (minimal) to 10 (most), with a mean change of 3.4 (95% CI 1.8-5.1, $P = .001$). In the 8 patients who experienced increased pain, the degree of pain worsening ranged from 3 to 10, with a mean change of 7.1 (95% CI 5.4-8.8, $P < .001$).

Retinoid dosing

Among the participants of this study taking oral retinoids the dose ranged from 10 to 50 mg/d (Table I). Forty percent of patients who were treated with doses of more than 25 mg/d (higher doses),

Table II. Questionnaire

Natural course of PC without treatment

- Did your PC condition change at times when not using any drug treatment?
- If yes, indicate range of change on scale of -3 (much worse) to $+3$ (much better), with 0 being your normal condition

Effectiveness/satisfaction

- Was drug effective?
- What was your overall satisfaction on scale of 1-10 (1 = lowest, 10 = highest)?
- Are you still using drug?
- Would you recommend drug to others?

Clinical treatment response

- While taking drug did your PC calluses/nails change?
- If yes, did calluses/nails get better or worse?
- If calluses/nails got better, what was improvement?
- What was clinical improvement/deterioration in your PC calluses/nails on scale of -3 (much worse) to $+3$ (complete improvement)?

Pain

- On scale of 0 (no pain) to 10 (worst pain you have ever experienced), rate your overall pain before taking drug
- While on drug, did you notice change in pain?
- If yes, did change cause more/less pain?
- If yes, indicate when change occurred
- If yes, mark change in your pain using scale of 1 (minimal) to 10 (most)

Dose and duration

- Which oral retinoid did you use (trade name)?
- If you remember, what dose or strength of medication did you use?
- How long did you take this medication?
- Was dose of your retinoid medication changed during treatment?
- If yes, to higher/lower dose?
- If yes, why was dose changed?
- Did change give more improvement?
- Did change create more adverse effects?

Adverse effects

- Did you experience any adverse effects?
- Did you experience any dry eyes/dry lips/dry skin/peeling of skin/hair loss/headaches/bone or joint pain/other adverse effects while taking drug?
- Did your doctor find any liver problems caused by use of retinoid treatment?
- Did you think improvement you experienced while taking drug was sufficient that you wanted to continue in spite of any adverse effects?
- Based on your experience, would you be interested in using oral retinoids again?

PC, Pachyonychia congenita.

reported overall effectiveness and a mean overall satisfaction score of 1.6 on a scale from 1 (lowest) to 10 (highest). In comparison, 73% of patients receiving oral retinoid doses of less than or equal to 25 mg/d (lower doses) reported overall effectiveness ($P = .14$) and a mean overall satisfaction score of 4.2 on a scale from 1 to 10 ($P = .02$). These results suggest that although lower doses are not significantly different in their effectiveness, the ratios among effectiveness, pain, and adverse effects were more favorable with lower doses. Decreased plantar pain during therapy with oral retinoids was reported in 50% treated with higher doses and 67% of patients treated with lower doses ($P = .53$), ie, higher retinoid doses were not superior in reducing pain.

Treatment duration

The duration of treatment with oral retinoids ranged from 1 to 240 months, with 50% of the patients receiving therapy for longer than 5 months (longer duration) and 50% less than or equal to 5 months (shorter duration) (Table I). Of patients who were treated for a longer duration, 67% reported overall effectiveness and a mean overall satisfaction score of 3.6 on a scale from 1 to 10 compared with 33% effectiveness ($P = .07$) and a score of 1.9 ($P = .06$) in the patients receiving oral retinoids for a shorter duration. An improvement of PC calluses was reported in 83% of patients treated longer than 5 months and 75% treated for 5 months or less ($P = .66$); the overall change in plantar hyperkeratosis on



Fig 1. A, Thick plantar hyperkeratosis in patient with pachyonychia congenita before treatment with oral retinoids. **B**, Thinning of calluses while on therapy with acitretin. However, medication had to be discontinued because of adverse effects, ie, peeling of skin and increased pain and vulnerability of feet when walking.

a scale from -3 (much worse) to $+3$ (complete improvement) was 0.7 for the longer duration group versus 0.3 for the shorter duration group ($P = .38$). A decrease in plantar pain was reported in 67% of patients treated for a longer period and 33% treated for a shorter duration, but this again was not statistically different ($P = .19$). Interestingly, the percentage of patients with increased plantar pain was lower in the group with longer treatment duration (33% vs 67%).

Retinoid classes

Only patients who had received acitretin ($N = 12$) or isotretinoin ($N = 14$) were further compared because of the small number of patients treated with etretinate or vitamin A (Table I). The overall effectiveness was 58% for acitretin and 36% for isotretinoin ($P = .26$), the overall satisfaction score was 3.5 for acitretin versus 2.1 for isotretinoin ($P = .14$). Ninety percent of patients in the acitretin group compared with 57% in the isotretinoin group reported thinning of calluses ($P = .13$) (Fig 1); the overall change on a scale from -3 (much worse) to $+3$ (complete improvement) was 0.9 versus -0.1 ($P = .05$). In all, 63% versus 50% experienced decreased plantar pain while on acitretin and isotretinoin, respectively ($P = .65$). Although not significantly different, these data indicate that acitretin may have a slight edge over isotretinoin in treating PC.

Adverse effects

All study patients experienced adverse effects. With the exception of one man all patients reported dry lips, 15 (50%) dry eyes, 27 (90%) dry skin, 11 (37%) peeling of the skin, 9 (30%) hair loss, 6 (20%) headaches, 5 (17%) bone or joint pain, 4 (13%) sun sensitivity, and one patient depression, fatigue, and developing of bone spurs, respectively. In one patient treatment with oral retinoids was stopped because of liver enzyme abnormalities.

Considering retinoid doses, ie, more than 25 mg/d versus less than or equal to 25 mg/d, the prevalence of adverse effects such as dry lips (90% vs 100% , $P = .29$), dry eyes (20% vs 64% , $P = .05$), dry skin (90% vs 91% , $P = .94$), skin peeling (50% vs 36% , $P = .54$), hair loss (20% vs 55% , $P = .11$), headaches (20% vs 18% , $P = .92$), and bone/joint pain (20% vs 36% , $P = .42$) was comparable. There was no difference in adverse effects relative to treatment duration and there was also no significant difference in adverse effects when comparing acitretin with isotretinoin.

Nine patients (30%) decided to continue treatment with oral retinoids despite adverse effects because they perceived PC improvement as sufficient. Based on their experience, 14 patients (47%) would be interested in using oral retinoids again, primarily because of the overall effectiveness they experienced. Sixteen patients (53%) would not use oral retinoids again. However, the question used for this assessment (Table II) did not address in detail

why patients stated that they would or would not want to use oral retinoids again.

Predictors of effectiveness

To identify additional patient subsets that might be more likely to benefit from oral retinoid treatment, we used logistic regression modeling. The calculated odds ratios were 0.13 for female versus male (95% CI 0.02-0.89), 1.6 for acitretin versus isotretinoin (95% CI 0.3-9.6), and 0.7 for age, per 10 years (95% CI 0.4-1.5). These results indicate that neither patient age nor retinoid type were predictors of effectiveness. In contrast, a benefit from oral retinoid treatment was less likely in female than in male patients.

DISCUSSION

The few available case reports and case series assessing therapy of PC with oral retinoids yielded contradictory results with a tendency toward more favorable outcomes with treatment. Dupré et al⁸ asserted improvement of PC calluses and decreased pain in 3 patients treated with an aromatic retinoid, Hoting and Wassilew⁹ reported a remission of palmo-plantar hyperkeratosis but no changes in pachyonychia in two patients treated with etretinate 75 mg/d and a relapse when reducing the drug to 30 mg/d after several months, Carabott et al¹⁰ described a patient who experienced reduced plantar hyperkeratosis after 3 months of etretinate therapy at a dose of 50 mg/d, and Lim et al¹¹ reported amelioration of calluses but not of nail changes in a patient treated with 30 mg acitretin daily. In contrast, two additional case reports did not show any clinical benefit for oral retinoids in the treatment of PC. Thomas et al¹⁴ reported a father and his son who did not show improvement of plantar keratoderma despite therapy with high doses of isotretinoin. Similarly, Soyuer and Candan¹⁵ described failure of etretinate in a child with PC, but the treatment was only administered for 5 weeks, and the dose had to be progressively lowered because of hypertriglyceridemia. Consistent with the contradictory findings in these published reports, in the current study involving 30 patients from the PC registry, oral retinoids resulted in thinning of calluses (decrease in hyperkeratosis) in only a subset of study patients.

A very important aspect of PC treatment is that thinning of calluses does not necessarily imply decreased plantar pain when walking, as reported for other types of palmoplantar keratoderma. In a family with keratoderma of the soles associated with blistering but lack of pachyonychia, treatment with isotretinoin resulted in callus reduction, but blistering worsened and pain increased.¹⁶ This was also observed by Fritsch et al,¹⁷ who described a dramatic

improvement of hereditary epidermolytic palmo-plantar keratoderma in 4 patients treated with an oral aromatic retinoid for 5 months, resulting in normal-appearing skin. However, therapy had to be discontinued as the vulnerability and sensitivity restricted normal function of hands and feet. In the current study roughly only one third of patients experienced improvement of pain although 50% of the patients reported improved plantar hyperkeratosis, ie, in some cases even though calluses thinned, there was increased pain.

Recently, mutations in *KRT6*, *KRT16*, and *KRT17* were correlated with characteristic clinical findings in patients with PC; ie, *KRT6B* was associated with increased pain intensity.¹⁸ When stratifying our patients by genotypes, because of the small subgroups, no further analysis regarding treatment effectiveness was possible.

This study has several limitations including its retrospective, cross-sectional study design, which is prone to a recall bias. Although the measurements were patient-based and subjective, ie, not assessed by a physician, the study end points are patient-centered in a positive sense, in that they should be highly relevant for reflecting patient perception of treatment. The lack of laboratory monitoring for potential adverse effects such as liver function testing may result in an overestimation of the benefit/risk ratio of the treatment modality, ie, our study design is biased to exclude patients with severe adverse effects. In the current study, discontinuation of oral retinoid therapy was only necessary in one patient because of elevated liver transaminases. This is in accordance with two previous studies, in which similar retinoid doses have been used for the treatment of various forms of ichthyoses and psoriasis, and no severe adverse effects were reported.^{12,13}

This study demonstrates a potential advantage of treatment with lower doses of acitretin for a longer duration compared with therapy with higher doses, shorter duration, and isotretinoin. Recently it was shown that in the treatment of patients with psoriasis low-dose acitretin (25 mg/d) was associated with fewer common adverse effects than high-dose acitretin (50 mg/d).¹³ Because lower doses may have a better risk/benefit ratio, it might be beneficial to begin treatment at a lower dose (eg, acitretin 10-25 mg/d) with further dose adjustments based on patient's response. Alternatively, treatment may be initiated at a higher dose and subsequently adjusted depending on pain and adverse effects. It is important that patients are fully informed about potential adverse effects before initiation of therapy including the possibility of increased pain when on oral retinoids.

In conclusion, the results of our study confirm that treatment of PC with oral retinoids is effective in some individuals with PC. Randomized, controlled, prospective clinical trials with both objective and patient-centered subjective end points are warranted to further define the patient subsets that most benefit from this treatment option.

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