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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.

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ORIGINAL ARTICLE

Best treatment practices for pachyonychia congenita

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Abstract

Background Numerous therapeutic modalities have been proposed to treat the manifestations of pachyonychia congenita (PC). While research hopes lie with molecular therapies, patients are in need of answers regarding the efficacy of conventional treatments.

Aim of the study To determine patients' experience and preferences regarding conventional treatments for PC.

Methods The study population included 120 PC patients from 20 countries. The study was based on a patient survey developed by physicians and researchers from the International Pachyonychia Congenita Consortium and conducted via the internet. Using an effectiveness scale of 1 to 5, the patients were asked to grade treatments for different manifestations, including keratoderma, cysts, follicular hyperkeratosis, fingernail and toenail involvement.

Results Patients reported surgical treatments being most effective for cysts and mechanical treatments the most effective conventional therapeutic approach for all other investigated manifestations. The other conventional medical treatments were found to be non-effective to only slightly effective. Among patients with keratoderma, older people were more likely to report beneficial effect from mechanical treatments ($P = 0.04$), topical retinoids ($P = 0.04$) and topical steroids ($P = 0.02$). Likewise, females were more inclined to report filing and grinding beneficial than males ($P = 0.02$). Finally, carriers of *KRT16* and *KRT6a* were more likely to benefit from keratolytics than carriers of mutations in *KRT17* ($P = 0.04$).

Conclusions None of the currently available therapeutic options for PC are ideal, although they provide some relief, with mechanical/surgical options being preferred over medical therapies. These results emphasize the need for more efficient and targeted therapies.

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Conflict of interest

None declared.

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Introduction

PC is a very rare keratinizing disorder estimated to affect between 5 and 10 thousand people worldwide.[1] This disorder is transmitted as an autosomal dominant trait, and is caused by mutations in one of five keratin genes: *KRT6A*, *KRT6B*, *KRT6C*, *KRT16*, *KRT17*, which encode keratins K6a, K6b, K6c, K16 and K17 respectively.[1,2] Most of the keratin mutations which cause PC are heterozygous missense mutations or small insertions/deletions which result in fragility of the epithelial cell cytoskeleton, leading to cell cytolysis and tissue blistering or hyperkeratosis.[2–4]

PC cardinal features were first reported by Muller[5] and Wilson[6] in 1904, and by Jadassohn and Lewandowski in 1906,[7] and include painful and debilitating plantar keratoderma, hypertrophic toenail and fingernail dystrophy, follicular hyperkeratosis, palmar keratoderma, epidermal cysts, oral leukokeratosis, and occasionally hyperhidrosis, hoarseness and natal teeth.[1,2]

Clinical classification of PC variants was first suggested by Kumer in 1935.[8] PC was eventually divided into two clinical subtypes: the Jadassohn-Lewandowski PC (type-1 PC) and the Jackson-Lawler PC (type-2 PC).[1,2]

This clinical classification was intended to assist estimation of the prognosis in the absence of genetic testing.[1,2] After the discovery of the underlying cause of PC, genotype-phenotype analysis suggested initially that mutations in KRT6a/KRT16 and KRT6b/KRT17 were associated with type 1 and type 2 PC respectively.[1] More recently, large-scale genetic analysis raised doubts regarding the clinical relevance of these correlations,[1,2] leading to the establishment of a novel classification for PC

based solely on molecular analysis resulting in PC-K6a, PC-K6b, PC-K6c, PC-K16 and PC-K17 as distinct types.[1,2]

Many therapeutic modalities have been proposed to treat the various clinical manifestations in PC, including retinoids,[9] surgical and mechanical procedures, orthotics, keratolytics, pain medications[10] and botulinum toxin.[11] Recently, more targeted therapeutic strategies (including small interfering RNAs,[12–14] rapamycin[15] and simvastatin[16]) have been the focus of much attention. Unfortunately, as most of these advanced approaches still cannot be offered on a routine basis to patients because of expense and limited availability, patients are currently forced to rely upon the use of the available conventional strategies.

In this study, we used a patient survey approach to derive effectiveness data in PC. This methodology has been widely used over the past years to delineate guidelines for the treatment of disorders for which no controlled data are available.[9]

Methods

Patients

The study population included pachyonychia congenita patients from 20 different countries who were enrolled in the International Pachyonychia Congenita Research Registry (IPCRR) and recruited through Pachyonychia Congenita Project, a non-profit patient advocacy group established in 2004.[1,2] All patients were diagnosed using a detailed clinical questionnaire and genetic testing results for a mutation in one of the PC-associated genes. The study was conducted according to the principles of the declaration of Helsinki and all patients gave their written informed consent.

Data collection

In addition to the extensive physician-validated data in the IPCRR, each patient completed an addendum survey via the internet providing information on treatments used for five categories of clinical manifestations of PC: keratoderma, cysts, follicular hyperkeratosis, fingernail and toenail involvement. In addition, all patients provided information on demographics, genetic status, the effect of the disease on their quality of life, the clinical manifestations of PC and the degree of effectiveness of the different treatments.

The patients were asked to grade each treatment they had used according to a treatment effectiveness scale of 1 to 5:

1- not effective at all
2- a little effective
3- somewhat effective
4- effective
5- very effective.

The patients were asked to grade different available treatments including mechanical treatments (such as filing, grinding, cutting, clipping or plucking the lesions), surgical removal of the lesions, surgical removal of the nail, incision and drainage of cysts, soaking of the nails to soften them before treatments, orthotics, custom made orthotics, topical and oral retinoids, pain medications, botulinum toxin, moisturizers, vaseline, keratolytic treatments, antibiotic ointments, antifungal ointments, topical and oral steroids, salicylic acid, treatments of the nails by medical professional and treatments of the nails in a nail salon.

Statistical analysis

All outcome variables are ordinal variables ranging from 1 to 5 – the higher the score, the higher the treatment effect. Univariate analysis was used to determine the relationships between each explanatory variable and the treatment outcome variables. The explanatory variables are the following: age, gender, quality of life score (QOL) and gene (categorical variable).

Pearson correlations were calculated between all continuous explanatory variables and the outcome variables. Wilcoxon Two-Sample or Kruskal–Wallis tests were used to compare between categorical explanatory variables and the outcome variables.

A *P*-value of 0.05 was considered significant. Statistical analysis was performed by SAS for windows version 9.2 (SAS Institute, Cary, NC, USA).

Results

The study included 120 PC patients, 67 females and 53 males, of all ages. The youngest patient was a 1-year-old baby and the oldest an 81-year-old patient. The average age was 38.5, and the median age was 39 years.

Keratoderma

Of the 120 patients who took part in the study, 113 patients reported having keratoderma. Forty-eight patients had clinical manifestations involving both palms and soles; 65 patients had only sole involvement.

Most conventional treatments were attributed mean scores of 2 to 3 (a little effective to somewhat effective) (Fig. 1). Patients reported mechanical treatments (such as filing, grinding, cutting, clipping), as the most effective conventional treatments corresponding to a mean score of 3.8. Pain control medications and orthotics ranked second in effectiveness.

Other medications such as antibiotic ointments, urea cream, oral and topical retinoids, oral and topical steroids, botulinum toxin injections, salicylic acid or antifungal treatments were reported as poorly effective.

Cysts

Of the 120 patients who took part in the study, 49 patients reported having cysts (Fig. 2). Surgical removal treatment was found to be effective to very effective, reaching a mean score of 4.32. The next most effective treatment reported was incision and drainage with a mean score of 4. Pain medications were

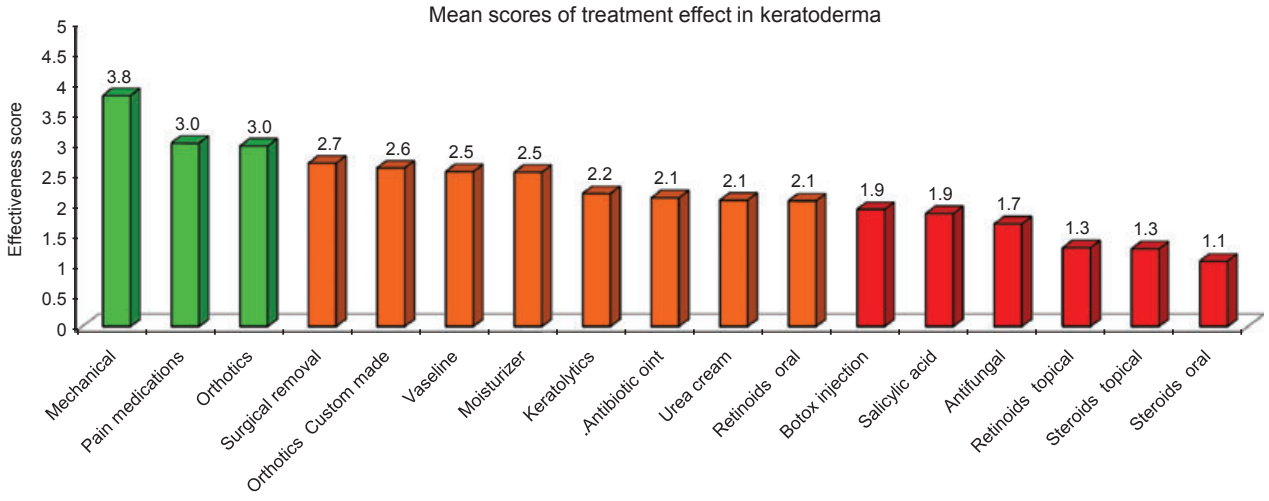

Figure 1 Mean scores of effectiveness of the different treatments used for keratoderma (reported by 113 patients). Treatment effectiveness is represented by a colour scale: red - not effective treatment (scores between 1 and 2), orange - mildly effective treatment (scores between 2 and 3), green - somewhat effective treatment (scores between 3 and 4), blue - effective treatment (scores between 4 and 5).

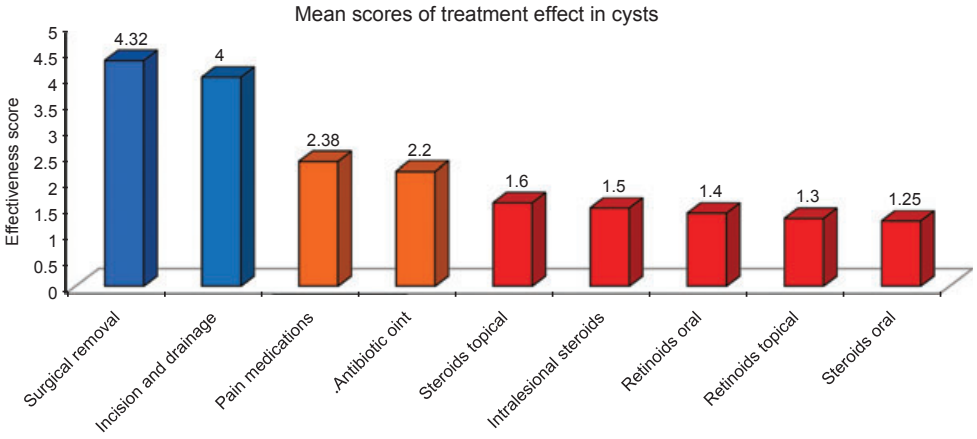

Figure 2 Mean scores of effectiveness of the different treatments for cysts (reported by 49 patients). Treatment effectiveness colour scale is described in figure legend 1.

found to be of little effect. Other treatments, such as antibiotic ointments, intralesional and oral steroids and retinoids, were reported as not effective.

Follicular hyperkeratosis

Of the 120 patients who took part in the study, 63 patients reported being affected with follicular hyperkeratosis. The results (Fig. 3) showed that the available conventional treatments for follicular hyperkeratosis were slightly effective or not effective, with clipping or plucking the plugs leading with a mean score of 2.9.

Toenail involvement

Toenail involvement is very common in PC. Of the 120 patients in the study, 108 patients reported toenail involvement. The results for toenail involvement (Fig. 4) demonstrated that the most effective approach was mechanical treatment such as filing, grinding, cutting or clipping the toenails. Mechanical treatment received a mean score of 4. The patients reported that the second most effective treatment, with a mean score of 3.6, was soaking the nails to soften them before treatment. Of note, surgical avulsion of the nail was found to be ineffective, as were non-medical treatments provided in nail salons.

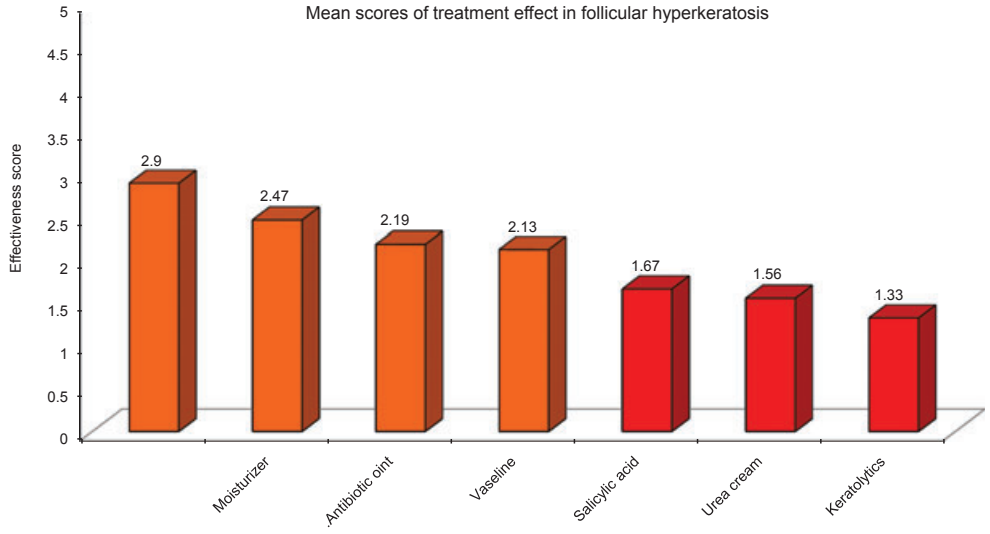

Figure 3 Mean scores of effectiveness of the different treatments used for follicular hyperkeratosis (reported by 63 patients). Treatment effectiveness colour scale is described in figure legend 1.

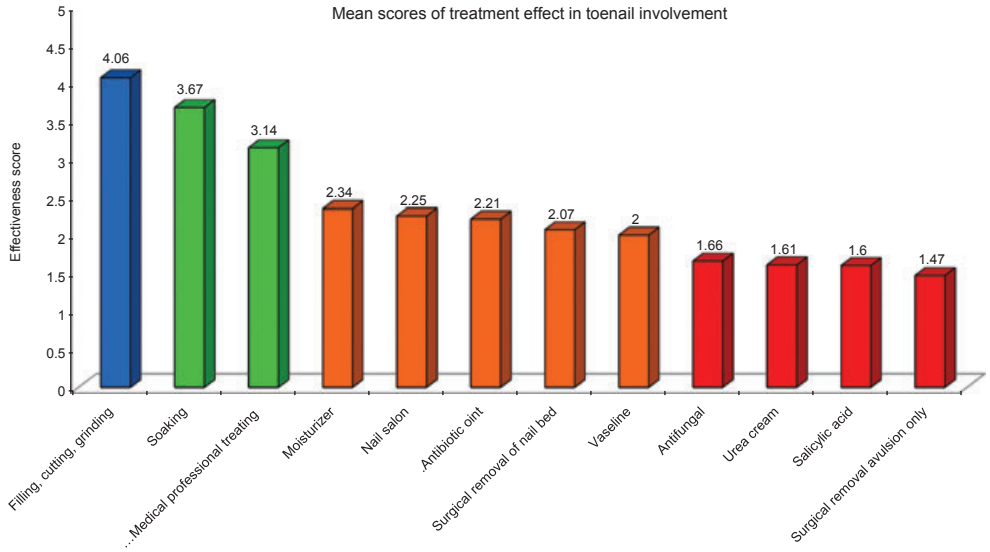

Figure 4 Mean scores of effectiveness of the different treatments used for toenail involvement (reported by 108 patients). Treatment effectiveness colour scale is described in figure legend 1.

Fingernail involvement

Fingernail involvement was reported by 94 of the 120 patients in this study. Results pertaining to fingernail involvement resembled those obtained for toenail involvement (Fig. 5).

The most effective treatment was mechanical treatment such as grinding, filing, clipping or cutting the fingernails. Mechanical treatments received a mean score of 4 and the second most effective treatment was soaking and softening the nails. The other treatments ascertained were found to be not effective.

Univariate analysis

As multivariate analysis was found to be very unstable due to the wide range of available data, we used univariate analysis to

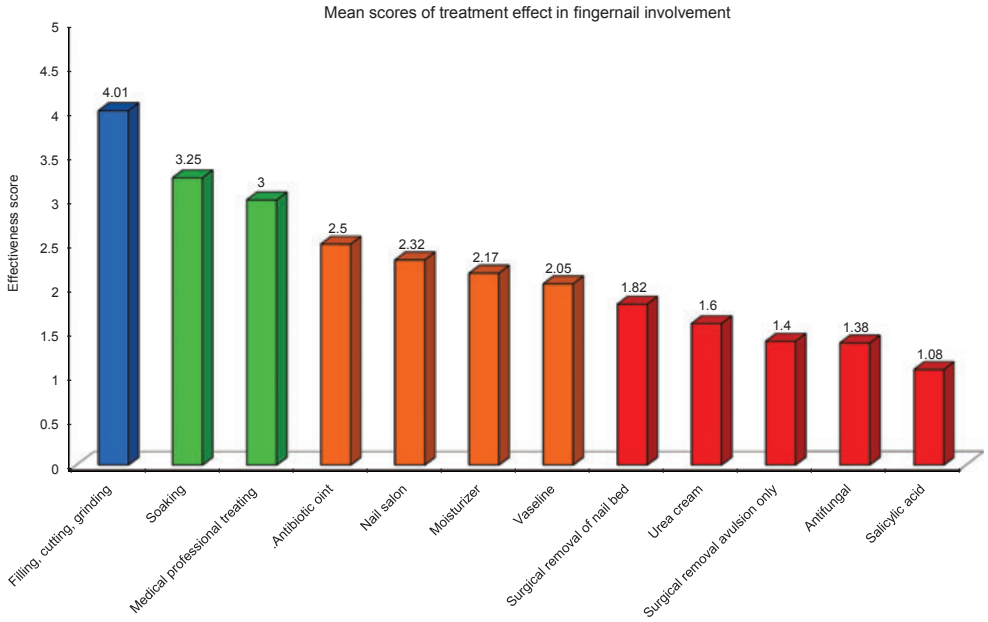

Figure 5 Mean scores of effectiveness of the different treatments used for fingernail involvement (reported by 94 patients). Treatment effectiveness colour scale is described in figure legend 1.

further analyse the data and to determine the relationships between each explanatory variable and the treatment outcome variables. This analysis revealed three facts of clinical relevance for patients with keratoderma:

1 As patients grew older, they were more likely to report beneficial effect from mechanical interventions (such as filing, grinding) ($P = 0.04$), topical retinoids ($P = 0.04$) and topical steroids ($P = 0.02$).
2 Females were more inclined than males ($P = 0.02$) to describe mechanical interventions such as filing and grinding as beneficial.
3 Finally, carriers of mutations in *KRT16* and *KRT6a* were more likely to benefit from keratolytics than carriers of mutations in *KRT17* ($P = 0.04$).

Discussion

Treating PC is challenging. PC is clinically multifaceted and the conventional treatments are directed at the different manifestations of the disorder. Currently, there are no specific treatments for PC.[16,17] Each patient presents a unique constellation of conditions and a treatment plan must be individually tailored.[17] Unfortunately, despite use of numerous approaches to relieve PC-associated symptoms, little is currently known regarding their relative efficacy.

Conventional treatment for nail disease in PC includes mechanical or surgical procedures, such as grooming or surgical removal of nails. The nails tend to re-grow unless complete ablation is performed. Follicular hyperkeratosis can be treated by oral and topical retinoids, keratolytic agents and alpha-hydroxy acid preparations. Cysts may be treated by incision, excision, drainage or by intralesional injection of steroids. In case of infection, oral antibiotics may be indicated.[10]

Currently, retinoids are considered efficient drugs to treat hyperkeratotic disorders including PC.[9,16] They act via retinoic acid response elements (RAREs) which are present in the keratin's gene promoters, and inhibit gene expression.[16] Retinoids, although reducing hyperkeratosis, may also cause thinning of the epidermis and blistering, leading to pain and possible infectious complications.[10,16,18] Contradictory data regarding the efficacy of retinoids in PC have been published. Some case reports demonstrated an improvement of calluses with retinoid treatment.[19–22] Other studies described patients with improvement of hyperkeratosis with retinoid treatment, but no change in pachyonychia.[21,22] More recently, Gruber *et al.*[9] analysed data collected in 30 PC patients who received systemic retinoid treatment. They found that 50% and 14% of their patients reported improvement in palmoplantar hyperkeratosis and pachyonychia respectively. The mean satisfaction score from the treatment was found to be 4.5 on a scale of 1–10. All patients reported suffering from adverse effects and 83% stopped using the drug.[9] In contrast with these mixed results, others have reported no improvement with retinoids in PC[23,24] and, in another series,[25] four patients with palmoplantar keratoderma who received oral retinoids reported improvement in the appearance of their skin, but

had to stop the treatment because of pain that restricted hand and foot function.

Levels of evidence vary according to the methodology used in clinical studies, which in turn is often a function of patient population size. Randomized control studies are of course preferable; however, in diseases as infrequent as PC, such studies are not always possible.[9,18] Alternative methodologies, also adapted to rare conditions in which controlled studies cannot be readily performed, rely upon the quantification of patient values and expectations.

Our study was based on a survey conducted among the largest group of PC patients ascertained to date for treatment efficacy. As all patients had been diagnosed with PC on the basis of both a careful physical examination and a full molecular analysis, we believe that the data collected faithfully reflect PC patients' appreciation of conventional therapeutic modalities.

We found that the majority of conventional treatments were only marginally effective for keratoderma, with mechanical treatments being the most effective.

Palmoplantar keratoderma is a very common manifestation of PC, usually presenting as a child starts walking and bearing weight during the first few years of life.[10] In a study by Eliason, *et al.*[1] plantar keratoderma was present in 241 of 254 (95%) of patients. Of the 13 patients reported as not having plantar keratoderma, the oldest was 3-years old and nine were younger than 1 year. Among 241 patients who reported having plantar keratoderma, the age of onset ranged from birth to 30 years and the average age was 4.2 years. In our study, most of the patients who did not report plantar keratoderma were younger than 5 years of age.

Patients reported surgical treatments being most effective for cysts. Mechanical treatments were found to be the most effective conventional therapeutic approach for follicular hyperkeratosis, as well as for toenail and fingernail involvement. The other conventional medical treatments were found to be non-effective to only slightly effective.

In line with a previous study,[26] keratolytics, which are widely used by the patients, were found to be of limited effectiveness for both palmoplantar keratoderma and nail problems.

Response to treatment was highly individual, underscoring the need for clinical or molecular predictors of response to therapy. In this regard, the results of our univariate analysis, which remain to be independently confirmed, suggest a number of such predictive parameters. For example, our finding that carriers of mutations in *KRT16* and *KRT6a* were more likely to benefit from keratolytics than carriers of mutations in *KRT17* may be explained by the fact that the latter group has milder keratoderma than the former groups.[1] This finding is consistent with phenotypic differences.

Overall, current available therapeutic approaches in PC are of borderline benefit. Therefore, the recent major advances in the search for PC-specific therapeutic strategies are of great importance. For example, a mutation-specific siRNA was found recently to lead to callus recession and pain control in a PC patient.[12–14,16] However, these injections were found to be tremendously painful underscoring the need for new approaches for more efficient and practical ways of nucleic acid delivery to the skin.[27] Other treatments under investigation for PC patients are rapamycin and simvastatin, but these therapies, although providing hope for patients, are not yet applied routinely.[10,15,16]

In conclusion, although none of the currently available therapeutic approaches seem to be ideal, they do provide some relief to our patients. Mechanical/surgical options are preferred over medical therapies, such as retinoids, antibiotics or antifungal agents. These results emphasize the need for more efficient and targeted therapies.

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