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Holistic Approach in the Treatment of Actinic Keratosis: Benefits and Disadvantages of 5-Fluorouracil, Imiquimod, Diclofenac and Curaderm

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Abstract

Background Actinic keratosis is the most prevalent premalignant skin disorder in the white population. Current guidelines provide no clear recommendations about preferred treatments. **Methods** The parameters; effectiveness, treatment duration, recurrence, side effects and cost of treatment were investigated for three frequently used topical therapies which were then compared with a most recent developed topical therapy. Published clinical data obtained from the literature was used to compare these parameters for 5-fluorouracil, imiquimod and diclofenac and relate them with the newly developed Curaderm. **Results** A wide variation in the concentrations of the active anti-keratotic ingredients, application frequency, duration of treatment, recurrence rates and cost of treatment exist between the different topical therapies. The efficacy rates and side effects were less variable. Overall, Curaderm is the most suitable treatment for actinic keratosis. Clinical evidence is presented illustrating the effects of Curaderm on field-directed treatments and solitary treatments of actinic keratoses. **Conclusions** Current medical guidelines do not provide clear recommendations on which treatment approach for actinic keratosis is preferred. Direct head-to-head comparison between treatments with emphasis on efficacy, safety, treatment duration, compliance, convenience, cosmetic outcome, patient acceptance and cost should be available to the patient, the practising physician, healthcare system and should assist in therapeutic treatment guidelines and policymaking. Given the very favourable profiles of these parameters with Curaderm when compared with other home-based treatments, it should be considered that Curaderm is first-in-line.

Keywords

Actinic Keratosis, Skin Cancer, 5-Fluorouracil, Imiquimod, Diclofenac, Curaderm, Efficacy, Recurrence, Cost

1. Introduction

Actinic keratosis (AK), also known as solar keratosis or senile keratosis is a precancerous skin growth and is a disorder of epidermal keratinocytes that is induced by the sun's ultraviolet light exposure or indoor tanning. This photoaging process can lead to an accumulation of oncogenic changes by inducing a mutation of the p53 tumor suppressor gene, which has been identified as a crucial step in AK formation. This tumor suppressor gene allows for cell cycle arrest when DNA or RNA is damaged. Dysregulation of the p53 pathway can result in unchecked replication of dysplastic keratinocytes, thereby serving as a source of neoplastic growth and the development of AK.

AKs characteristically appear as thick, scaly, or crusty areas that often feel dry or rough. Because of their rough texture, AKs are often easier to feel than to see, and the texture is sometimes compared to sandpaper. AKs are usually small lesions and commonly range between 2 and 6 millimetres, but they can grow to several centimetres in diameter. They may be dark, light, tan, pink, red, a combination of all these, or have the same colour as the surrounding skin.

There are several variants of AKs often characterized as: classic, hypertrophic (or hyperkeratotic), atrophic, AK with cutaneous horn, pigmented AK, actinic cheilitis, and Bowenoid AK.

AKs are often found in areas that are commonly sun-exposed, such as the face, ears, neck, scalp, chest, back of hands, forearms, or lips. A biopsy or excision is considered for definitive diagnosis by histologic examination of the lesion tissue.

1.1. Prevalence of Actinic Keratosis

The epidemiology of AK varies throughout the world according to the general makeup and skin type of the population and their lifestyle habits, specifically time spent in the sun.

In the year 2020 the population in the US was approximately 329 million, consisting of 167.5 million females and 162.4 million males. During that year, 10.2% of the female population, corresponding to17.09 million, had AK. Similarly, there were 162.4 million males of which 26.2%, corresponding to 43.04 million suffered with AK. So, the total incidence rate of AK in the US for the year 2020 was over 60 million. Moreover, 10% of people aged between 20 and 30 years and 90% of people over 80 years old in the US have AK. Its incidence is increasing because of the rising of the aging global population with chronic lifetime sun exposure. In Australia, the prevalence of AK is worse, and is estimated

to be 37% - 55% of Australian adults over the age of 40 [1]. Thus, AK is a skin disorder of epic proportions and requires urgent attention.

AK is typically asymptomatic, and no disease occurs. AK is defined as a precancer and may never become malignant. However, about 10% of AKs eventually become malignant squamous cell carcinoma (SCC), and indeed, the majority of SCCs do begin as AKs. Metastasis of cutaneous SCC is rare. Nevertheless, certain tumor and patient characteristics increase the risk of metastasis to 3% - 9% [2].

The longer people live, the more likely they are to develop skin cancer, and the greater their chances of dying from it. Although relatively rare, metastatic cutaneous SCC is potentially deadly, accentuating the requirement for its serious attention.

Not surprisingly, AK is increasingly one of the most commonly encountered challenges in dermatology. There are various treatment methods available, including topical creams, photodynamic therapy (PDT), cryotherapy, and laser ablation. Despite the numerous treatments available, AK remains an unsolved chronic condition. To date, there is limited studied evidence comparing different treatments, their long-term outcomes and treatment costs. Newer treatments with higher efficacy, lower side effects, lower recurrence rates, more cost-effective and patient-friendly therapies are necessary to adequately challenge AK.

Most recently, in 2018, a novel product Curaderm, was registered by the Decentralised European Authorisation Member State Mutual Recognition Procedure for the indication "Topical treatment with keratolytic action, and antineoplastic activity in the treatment and healing of localized basal cell carcinoma of the skin". The off-label indication is for the treatment of AK.

It is important to compare any new treatment with existing treatments for the identical medical condition in terms of safety, efficacy, recurrence, patient acceptability and cost.

Each of the current topical treatment-options varies in their dosing, efficacy, safety, recurrences and cost. Limited direct comparisons of the various topical treatments indicated for AK are available. Accordingly, knowledge of an indirect comparison of the relative safety, efficacy, patient-friendly and cost of topical treatments could be extremely helpful in informing health professionals. The overall objective of this communication is therefore, to compare the relative safety, efficacy, long-term outcome and costs of the most widely used self-administered, home-based topical treatments for AK and relate these findings to the recently approved Curaderm treatment.

1.2. Management of AK by Self-Administered, Home-Based Topical Medications 5-FU, Imiquimod, Diclofenac Gel and Curaderm

A variety of topical medication treatment options for AK are available. The selected choice of treatment depends on the patient and the clinical characteristics of the lesion. Besides safety and efficacy of a treatment regimen, the patient pre-

ference, lifestyle and costs are also important factors in determining the management plan for AK.

1.3. Comparison of the Mechanism of Action of 5-FU, Imiquimod, Diclofenac and Curaderm

1.3.1. Fluorouracil Cream

Fluorouracil (5-FU), an antimetabolite drug, is a uracil pyrimidine analogue with a fluorine atom at the C-5 position, irreversibly inhibits thymidylate synthetase (which normally converts deoxyuridine to thymidine) leading to the prevention of DNA replication and RNA synthesis. 5-FU in a topical cream prevents the proliferation of dysplastic cells in AK.

5-FU interferes with a cell's ability to reproduce. The AK precancerous skin cells multiply more frequently than normal cells. As a result, they absorb 5-FU faster than the surrounding healthy cells. The efficacy and safety of 5-FU depend on how much faster pre-cancer and cancer cells divide compared with normal cells. However, normal cells that reproduce are also destroyed by 5-FU. Drug resistance has greatly affected its clinical use [3]. Drug resistance is when cancer cells don't respond to a drug that usually is able to kill them. Drug resistance can lead to cancer or precancer treatment not working or to the cancer or precancer recurring.

1.3.2. Imiquimod

Imiquimod stimulates the innate and acquired immune responses, which ultimately lead to inflammatory cell infiltration, followed by apoptosis of diseased tissue. Topical imiquimod is an immune response modifier and cytokine (Interferon) inducer, it up-regulates cell-mediated immunity which is effective against viruses, tumors and AK. The mechanism of action of imiquimod, a toll-like receptor-7 agonist, is believed to be related to its ability to augment both the innate and acquired arms of immunologic responses [4]. This results in immunologic cellular infiltration directed at the site of the targeted antigen in the region where imiquimod is applied, such as on the keratotic lesion.

1.3.3. Diclofenac Sodium Gel

Topical diclofenac sodium gel is a nonsteroidal anti-inflammatory drug (NSAID) that is considered to work in the treatment of AK through inhibition of the arachidonic acid pathway, thereby limiting the production of prostaglandins, which are involved in the development of AK. Its mode of action in treating AK is not fully understood. It is thought that diclofenac blocks cyclo-oxygenase-2 (COX-2) [5] and reduces angiogenesis and cellular proliferation. It is believed that diclofenac starves the dysplastic keratinocytes resulting in apoptosis.

1.3.4. Curaderm Cream

Topical Curaderm cream contains the antineoplastic component BEC which is a mixture of solamargine, solasonine and mono-and diglycosides of solasodine. These natural glycoalkaloids seek out and destroy cancer cells by the process of

apoptosis. In addition to causing apoptosis in cancer cells and in hyperkeratotic cells, BEC also stimulates lasting immunity against cancer. The triglycoside solamargine in BEC is 9 times and 19 times more effective against cancer than the triglycoside solasonine and mono-and-diglycosides of solasodine respectively. BEC in Curaderm identifies pre-cancer and cancer cells by interacting with specific receptors that are present on these cells. Normal non-cancer cells do not possess these receptors and are therefore not affected by Curaderm. BEC enters the pre-cancer and cancer cells by a process known as receptor-mediated endocytosis, followed by the anticancer sequelae of identifiable anticancer properties on a variety of biological pathways, including cell survival pathways [6], tumor suppressor pathways [7], lysosomal pathways [8], mitochondrial pathways [9], caspase activation pathways [10], death receptor pathways [11], protein kinase pathways [12], and signal pathways that impede invasion/migration [13] [14] and multidrug resistance [13] [15].

Little information is available that quantifies the medication that is required to treat a single AK lesion and/or field-directed multiple lesions that are located in a continuous area. In this article it is shown that a very small quantity of Curaderm is required to treat AKs at various locations, including sensitive areas, and high density AKs per area.

Dermatologists and other health care professionals should identify high value treatment options and pathways of care for AK. Implementing these important pathways of care is a challenge and a necessity for healthcare reform.

This review addresses and delineates current, noninvasive strategies and relates these strategies with a most recent developed topical therapy for the treatment of AK.

2. Materials and Methods

Eighteen years of published medical literature (2005-2023) was evaluated using PubMed and Google Scholar databases. Noninvasive treatment modalities were examined, with particular emphasis allocated to the collection of data on 5-fluorouracil, imiquimod, diclofenac and Curaderm therapies in the care and management of actinic keratosis therapy.

Curaderm was manufactured and supplied by Curaderm Global Limited. The active ingredient in Curaderm is 5 mg% BEC (solasodine glycosides). Curaderm also contains salicylic acid, urea and lactic acid in a cetomacrogol cream base.

Curaderm cream was applied as a layer (approximately 50 - 100 microliters) to the lesions twice daily without a dressing during the day and with a dressing (micropore paper tape) at night-time [16] [17]. The field-directed multiple lesions in a continuous area required a larger quantity of cream depending on the area being treated. The function of the dressing with micropore tape of the treated lesion at night-time was to prevent rubbing-off of the cream during sleep. When treating other malignant skin cancers (basal cell and superficial squamous cell carcinomas) that require longer treatment periods (weeks), the

dressing with microtape during day and night is required to enhance absorption and drying out of the applied cream.

3. Results

Therapies of Home-Based Topicals

The regimens for self-administered, home-based topicals vary and may require once or twice daily applications for periods ranging from 3 days up to 16 weeks. Table 1 illustrates the frequency, treatment duration and composition of various brands of topicals.

There is a wide variation in the concentrations of the active anti-keratotic ingredients ranging from 5 mg% (Curaderm) to 5% (Aldara) in the different formulation brands. This also applies to the treatment frequencies and duration of treatment. The shortest treatment period was for Curaderm (3 - 5 days) and longest for Zyclara (16 weeks) and Solaraze (90 days).

The efficacy, recurrence rates and side-effects of home-based topical treatments of 5-FU, imiquimod, diclofenac and Curaderm are represented in Table 2.

Table 1. Frequency, treatment duration and composition of various brands of topical.

Active Principle	Brand	Quantity	Treatment Frequency and Duration
5-Fluorouracil	Fluoroplex	30 g of 1%	Twice daily for 2 to 6 weeks
	Tolak	20 g of 4%	Once daily for 4 weeks
Imiquimod	Aldara	12 Packets of 5%	Once daily, 5 days weekly for 6 weeks
	Zyclara	7.5 g of 3.75%	Once daily, 2 weeks cycles for 16 weeks
Diclofenac	Solaraze	100 g of 3%	Twice daily for 60 to 90 days
BEC	Curaderm	10 g of 5 mg%	Twice daily for 3 - 5 days

Table 2. Efficacy, recurrence rates and side effects of home-based topical treatments of actinic keratosis.

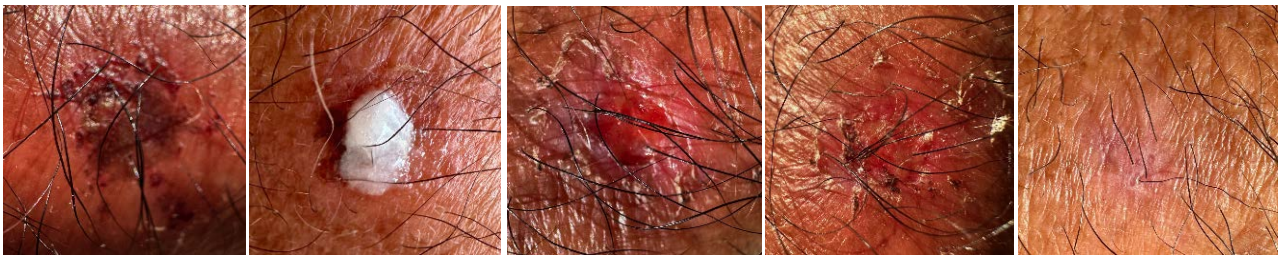
Active Principle	Efficacy %	Recurrence %	Side Effects	References
5-Fluorouracil	50	52	Pain, ulceration, redness, swelling, crusting irritation	[18] [19] [20] [21]
Imiquimod	50	20	Erythema, flaking, scabbing, erosion, pruritus, flu-like feeling	[20] [21] [22]
Diclofenac gel	40	85	Rash, redness, pruritus, dryness	[23]
Curaderm^{BEC}	82	7	Erythema, minor pain, erosion, swelling, flaking, pruritus	[16] [17] [24] [25]

The efficacy of the active anti-keratotic components is similar for 5-FU, imiquimod and diclofenac. Curaderm achieved the highest efficacy. The recurrence rates varied more widely and were highest for diclofenac and lowest for Curaderm. Lesion recurrence rates were evaluated 12 months after the end of treatment time. The side effects between the various anti-keratotic ingredients were generally similar.

Table 3 shows the cost without insurance rebates and commercially available packet sizes of various formulations of 5-FU, imiquimod, diclofenac and Curaderm.

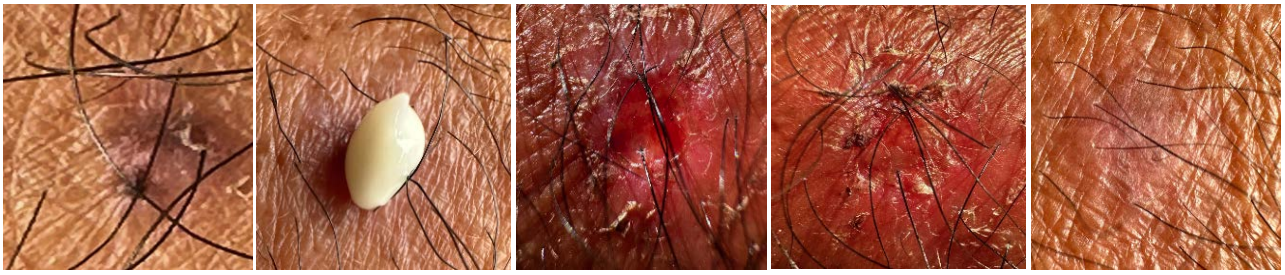
The packet sizes ranged from 7.5 g to 100 g. Little information is available to determine the true cost-efficacy, as defined as quantity of medication required to remove single solitary AK and/or field-directed multiple lesions in a continuous area. A big difference in the price of these medications is apparent, both within the same product, and when compared among different products. The prices of the products are governed by their packet size, which in turn is governed by the duration time of treatments. Topical creams or gels are usually a one-time purchase and applied at home on a specific regimen prescribed by the doctor and may need to be repurchased based on the treatment effectiveness.

Various Curaderm-treated solitary AKs (Figures 1-4) and field-directed AKs (Figure 5) are illustrated emphasising the minimal amount of cream required, the short treatment duration and the cosmetic outcome of the treatment.



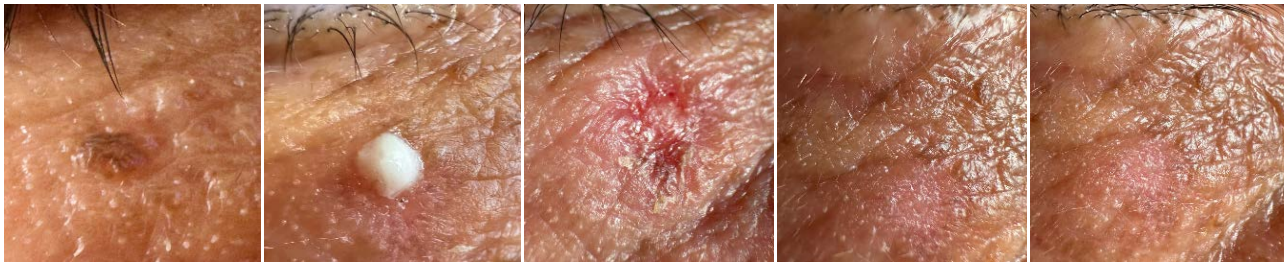
(a) (b) (c) (d) (e)

Figure 1. Illustrates an isolated AK (6 mm diameter) on the left arm before commencement of treatment (a), amount (100 microliters) of Curaderm applied to AK (b), after 6 applications of Curaderm (end of treatment, EOT) (c), 5 days after EOT (d), 14 days after EOT (e).



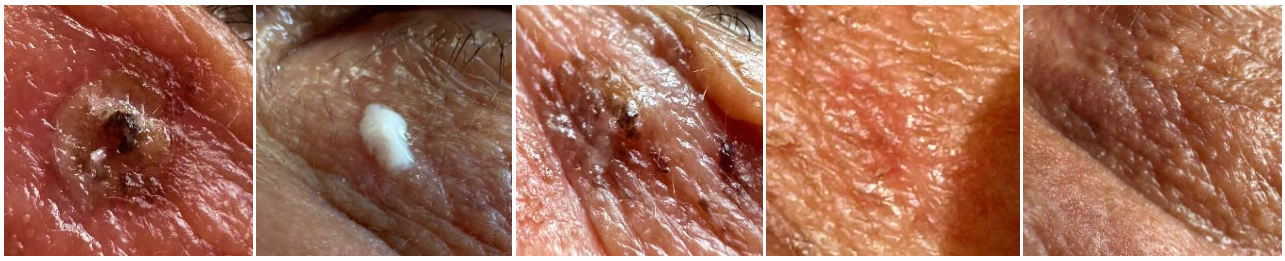
(a) (b) (c) (d) (e)

Figure 2. Illustrates another isolated AK (6 mm diameter) on the right arm similar to Figure 1.



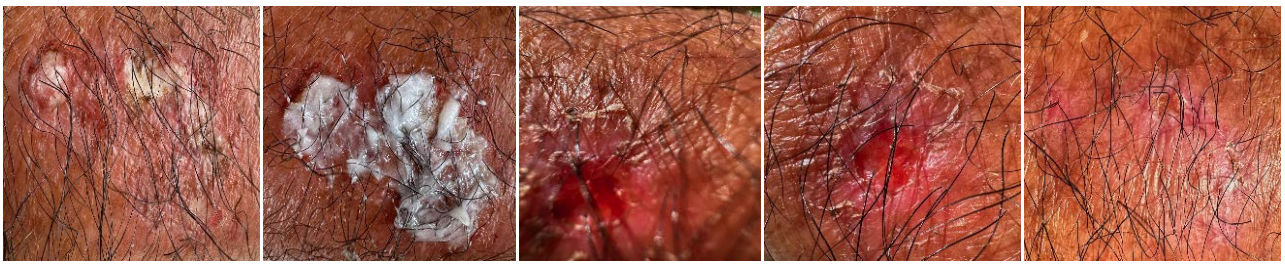
(a) (b) (c) (d) (e)

Figure 3. Shows an isolated pigmented AK (5 mm diameter) at zone 2 of the right orbital area before commencement of treatment (a), amount (80 microliters) of Curaderm applied to AK (b), after 6 applications of Curaderm, EOT (c), 3 days after EOT (d), 14 days after EOT (e).



(a) (b) (c) (d) (e)

Figure 4. Shows another isolated pigmented AK (5 mm) at zone 2 of the left orbital area similar to **Figure 3**.



(a) (b) (c) (d) (e)

Figure 5. Illustrates field-directed multiple (6) AKs located in a continuous area (12 mm × 10 mm) before commencement of treatment (a), amount (500 microliters) of Curaderm applied to the continuous affected area (b), after 6 applications of Curaderm, EOT (c), 3 days after EOT (d), 14 days after EOT (e).

Table 3. Packet sizes and cost without insurance of home-based topical treatments of actinic keratosis.

Active Principle	Brand	Pack Size	Price per packet (USD $)
5-Fluorouracil	Fluoroplex	30 g	1086.30
	Tolak	20 g	311.29
Imiquimod	Aldara	12 packets	125.01
	Zyclara	7.5 g	1355.18
Diclofenac	Solaraze	100 g	1748.00
BEC	Curaderm	10 g	100.00
		20 g	198.00

The figures show that the effect of Curaderm therapy occurs in various phases:

- Inflammation phase - Day 2
- Erosion phase - Days 2 to 4
- Healing phase - Days 4 to 14

The total quantity of Curaderm cream required to treat all AK lesions (4 solitary and 6 field-directed) was 5 grams.

4. Discussion

Abnormal gene expression correlates with the progression of normal skin to AK to SCC. Pathogenesis of AK includes alterations in the pathways regulating cell growth and differentiation, inflammation and immunosuppression caused by UV radiation, tissue remodelling, oxidative stress, and impaired apoptosis.

Substances that can prevent or affect these pathological pathways may potentially be suitable as a treatment for AK. For example, 5-FU interferes with the cell's ability to reproduce. Its efficacy relies on the rate of abnormal cell turnover relative to comparable normal cell turnover. The bigger the difference between abnormal and normal cell turnover, the higher the efficacy of 5-FU. In the case of AK these differences appear to be moderate, resulting in relative moderate efficacy rates, long treatment periods and high recurrence rates [18] [19] [20] [21].

Imiquimod is an immune response modifier. It counter balances the acquired immunosuppression and inflammation induced by UV exposure and enhances the innate immunologic response resulting in regression of AK. The efficacy rate of imiquimod is moderate but the treatment time is long. Because of its mode of action and the required treatment period, the recurrence rate is moderate [20] [21] [22].

Diclofenac gel, a nonsteroidal anti-inflammatory drug, is considered to block cyclo-oxegenase-2 (COX-2) and reduces angiogenesis, slowly starving and reducing cellular proliferation. This possible mode of action of diclofenac gel yields low efficacy, long treatment times and high recurrences [21] [22] [23].

The glycoalkaloids in BEC specifically induce apoptosis, a process of programmed cell death, in a wide range of systemic cancer cells and skin cancers [24]-[30] with high therapeutic indices [31]. This is reflected by the high efficacy rates and low side effects when treating AK with Curaderm. BEC in Curaderm also stimulates lasting immunity against cancer and may explain the low recurrence rate of AK with Curaderm therapy [16].

Apoptotic cells do not stimulate inflammation, non-the-less, inflammation is observed when Curaderm therapy is applied to premalignant AK and the malignant skin cancers, basal cell carcinomas (BCCs) and SCCs. However, placebo arms with Curaderm studies show clearly that the inflammation is caused by the excipients and not BEC in the formulation [16]. Curaderm loosens and tears apart desmosomes by extracting desmogleins and disrupts cellular junctions. Curaderm also breaks hydrogen bonds between susceptible molecules leading to

structural destabilisation of secondary and tertiary structures of the intercellular matrix of the cells of the skin. These cellular structural alterations result in improved bioavailability and efficacy of BEC to interact with cancer cells and actinic keratotic cells [32]. However, it cannot be ruled out that necroptosis which is a programmed form of cell death that bears a mechanistic resemblance to apoptosis and a morphological resemblance to necrosis occurs with Curaderm therapy.

A limitation with this communication is that not many studies are available to directly compare the various described parameters, in particular the quantity of medicine required to effectively treat AKs.

Attempt to address this shortfall was recently reported whereby cost per patient, but not per lesion, was €99.0 for diclofenac and €140.9 for imiquimod [33].

Figures 1-5 show that low quantities of Curaderm are required to effectively treat AKs with resultant impressive cosmesis. Importantly, the recurrence rate of Curaderm treated AKs with a follow-up period of one year, is only 7% [16]. Less than 5 grams of Curaderm eliminated 4 solitary AKs and 6 AK lesions that were located in a continuous area. This translates to a treatment cost of US $5.00 per one keratosis (**Table 3**). This is much lower than the costs for cryotherapy and other topical treatments [34].

The determining phenomena with Curaderm treatment are:

- highly effective (essential as a treatment)
- safe with low side effects (convenient for the patient)
- short treatment time (ensuring high compliance)
- small quantity of Curaderm required (low cost)
- rapid healing (patient acceptability)
- excellent cosmetic outcome (improves patient confidence)
- relevant for sensitive parts of the body (wide applicability)
- low recurrence (confidence in treatment)

In a clinical setting it is important to have a suitable health-care professional supervise the treatment of AK and it is not essential to involve a specialist dermatologist. An average American dermatology appointment wait is 32.3 days. This restriction is considered to be too long to wait for an appointment and is crucial for the patient who may be concerned for their health and would prefer more timely advice for their condition. Such advice can be supplied by any health-care professional. Therefore, it is advantageous to have available a treatment that does not necessarily require a dermatologist appointment.

5. Conclusion

For an accomplished treatment of AK, assessment of cure rate, safety, convenience, compliance, cosmetic results and cost-effectiveness should be considered. Given the very favourable profiles of these parameters with Curaderm when compared with other home-based treatments, it should be considered that Curaderm is first-in-line.

Declaration

Dr Cham holds patent rights on BEC technology.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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