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Efficacy of Zyclara Cream (3.75% Imiquimod) Once a Day for one Week in Actinic Keratosis of the Face: Results From a Non-Randomized, Open-Label, Prospective Study

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Abstract

Scope: Actinic keratoses are premalignant lesions of the epidermis that result from ultraviolet radiation exposure and can advance into squamous cell carcinoma. 3.75% imiquimod cream, available as Zyclara, is an immune response modifier that has been demonstrated to be an effective alternative to conventional treatment for actinic keratosis. The objective of this study was to collect data on ten patients with multiple non-hypertrophic facial actinic keratoses following the daily week long topical application Zyclara cream, in order to analyze its effectiveness and safety in a shorter treatment duration than standard approaches.

Methodology: This non-randomized, open-label, prospective study enrolled ten participants 18 years of age or older with actinic keratoses presenting on their face or scalp and were instructed to apply topical Zyclara cream once daily for seven days. All patients were examined by the study dermatologist at the end of treatment to record adverse effects and treatment ease of use. Follow-up patient visits took place at 4 weeks, 8 weeks, 6 months, and 12 months to track possible actinic keratosis recurrence and side effects.

Findings: All patients described relatively easy treatment use with 70% reporting very easy use. At 8 weeks following treatment, 37.5% of patients demonstrated complete clearance, while 62.5% showed partial clearance. At 12 months, 14.3% of patients demonstrated complete clearance, 71.4% showed partial clearance, and 14.3% had no clearance. Adverse events were minor with localized erythema and other cutaneous reactions being most common. No serious adverse events were reported.

Conclusion: These findings suggest that daily, week long imiquimod application in the form of 3.75% Zyclara cream is a safe and well-tolerated treatment that can decrease the recurrence of actinic keratoses.

Limitations: Three main limitations of the study were noted. Non-randomization increased the impact of patient and investigator bias, leading to a potential overexaggeration of reported results. Extraneous variables could not be accounted for due to the lack of a comparator group. Finally, there was diminished accuracy in AK recurrence rate from the small sample size and having follow-up data only until 12 months post-treatment.

Keywords: Actinic keratosis • Zyclara • Imiquimod • Daily treatment • Clearance rate • Tolerability • Ease of use

Introduction

Actinic Keratoses (AKs) are dysplastic epidermal keratinocytes [1,2]. They arise due to excessive exposure to Ultraviolet (UV) radiation as solar radiation promotes damage response pathways in keratinocytes and can suppress the immune system. AKs often are termed precancerous or premalignant as lesion extension into the dermis can result in keratinocyte carcinomas such as Squamous Cell Carcinoma (SCC), with potential for its subsequent metastasis [3-6].

Increased prevalence of AKs has led to it being one of the most common dermatologic presentations. Rates of occurrence vary geographically, as up to 25% of adults in the northern hemisphere and up to 60% of adults in Australia experience one or more AKs in their lifetime [7,8]. Susceptibility risk factors include cumulative UV

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radiation exposure, advanced age, fair skin, immunosuppression, predisposing genetic disease, and a previous history of AKs. Diagnosis can be clinical with the presence of skin coloured to red-brown scaly or hyperkeratotic papules or plaques [9]. AK development can be most seen on sun-exposed areas of the body, such as the face, ears, neck, forearms, dorsal hands, and balding scalp [10].

Current treatment methods often involve cryosurgery, curettage, or topical 5-fluorouracil. Less common methods include surgical excision, electrosurgery, laser ablation, photodynamic therapy, and chemical peels [11]. Immunological response enhancers are also viable treatment options [12]. As such, topical imiquimod cream has been approved as an effective treatment for AKs, with current recommendations for its application stating two 2 weeks treatment cycles separated by a 2 weeks no treatment period [13].

Imiquimod is available as 3.75% Zyclara cream. It is an imidazoquinolinone amine that acts as an immune response modifier of both the innate and adaptive branches of the immune system. Functioning as a proposed toll like receptor 7 agonist, imiquimod has demonstrated its effectiveness in increasing the production of interferon-α, interferon-γ, interleukin-12, and tumour necrosis factor-α [14-17]. This results in an increase in the number of antigen-presenting cells, inducing a cytokine cascade and causing subsequent cytotoxic T-lymphocyte differentiation and proliferation.

As imiquimod use in AK treatment is still a relatively new therapeutic option, further research is needed to determine its exact pharmacodynamic profile and effectiveness. There is also a need to enhance patient tolerability of imiquimod to minimize adverse events. Therefore, this study was conducted to advance existing research on using topical imiquimod cream to treat AK and decrease side effect occurrence using a novel, shorter treatment duration approach.

Meterials and Methods

We conducted a prospective case series at simcoderm medical and surgical dermatology centre over the span of one year. Ten patients (5 M, 5 F) with multiple non-hypertrophic facial Actinic Keratoses (AKs) were enrolled in this non-randomized, open label, prospective study. Subjects were 18 years of age or older with AKs of the face or scalp. They were excluded if they had hypersensitivity to imiquimod or any component of the treatment. Patients were enrolled only after their informed consent was obtained, and the study was approved by the Canadian SHIELD ethics review board. After a baseline assessment for facial AKs, the treatment (3.75% Zyclara cream) was given to all participants with instructions that it should be applied once daily for a total duration of seven days, as per study indication to evaluate a shortened treatment duration. The second visit was conducted on day 7 of the study, corresponding with the end of treatment. Patients were examined for adverse events (Table 1) and treatment ease of use. Further visits were conducted at 4 weeks, 8 weeks, 6 months, and 12 months, as recommended by the investigating dermatologist, during which the number of AKs and possible side effects of treatment were recorded.

Ease of use was defined subjectively by patients on a scale of 1-10 (1 very easy, 10 very hard) during their second visit. If the patient reported a range of values, the higher end of the range (higher difficulty) was used in the analysis. Complete clearance was defined as a total absence of facial AKs compared to baseline, as observed by a dermatologist during follow-up visits. Similarly, partial clearance was defined as a decrease in the number of facial AKs compared to baseline. Adverse events were determined through a mix of objective examinations by a dermatologist and subjective reports by patients during their second visit, and each subsequent visit.

Results

Two patients were excluded from the final analysis; one patient was lost to follow-up by week 4, and one did not have facial AKs by their first visit. Seven patients (70%) reported that the treatment was very easy to use (Table 2). 37.5% of patients demonstrated complete clearance at 8 weeks, while 62.5% showed partial clearance at this time (Table 3). Complete clearance and partial clearance at 12 months were 14.3% and 71.4%, respectively (Table 4). Two patients who showed partial clearance at 8 weeks, experienced late complete clearance at 6 months, with one of the two experiencing recurrence by 12 months. No patient had a serious adverse event.

Localized erythema was the most common adverse event, present in all participants, with pruritus being the second most common (8/9), followed by edema (6/9) (Table 5). Any adverse events that were reported on day 7 (Visit 2) were resolved by day 14 (Visit 3).

Symptoms
General skin reaction: Localized erythema, flaking, scaling crusted skin, skin sclerosis, dermal ulcer, localized vesiculation, excoriation, edema, site discharge, pruritus, burning, localized blanching, cold sores.
Generalized symptoms: Fungal infection, upper respiratory infection, chest pain, headache, fatigue, dizziness, local soreness, rigors, anxiety, pain, tingling, eczema, cheilitis, alopecia, dermal hemorrhage, rash, tinea cruris, swollen lymph nodes.
GI symptoms: Nausea, diarrhea, anorexia, vomiting, dyspepsia, mucosal ulcers.
GU symptoms: Vaginal itching or discharge.

Table 1. List of adverse events assessed by the study dermatologist after 7 days of zyclara treatment for facial AKs.

Difficulty of Treatment (1-10)*	Frequency (%)
1	7 (70%)
3	2 (20%)
4	1 (10%)

*1=very easy, 10=very hard

Table 2. Ease of use of treatment as reported by patients after 7 days of zyclara treatment for facial AKs.

	Male # (%)	Female # (%)	Total # (%)
Complete clearance	2 (50.0%)	1 (25.0%)	3 (37.5%)
Partial clearance	2 (50.0%)	3 (75.0%)	5 (62.5%)
No clearance	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 3. Complete and partial clearance of facial aks at 8 weeks following 7 days of zyclara treatment for facial AKs.

	Male # (%)	Female # (%)	Total # (%)
Complete clearance	0 (0.0%)	1 (25.0%)	1 (14.3%)
Partial clearance	3 (100.0%)	2 (50.0%)	5 (71.4%)
No clearance	0 (0.0%)	1 (25.0%)	1 (14.3%)

Table 4. Complete and partial clearance of facial aks at 12 months following 7 days of zyclara treatment for facial AKs

Symptoms	Frequency (/9)
Localized erythema	9
Pruritus	8
Edema	6
Scaling crusted skin	4
Excoriation	4
Burning	4
Flaking	2
Headache	2
Local soreness	2
Site discharge	1
Fatigue	1
Tingling	1
Rash	1
Nausea	1
Diarrhea	1

Table 5. Adverse events reported by patients after 7 days of zyclara treatment for facial AKs.

Discussion

The results from this study show that imiquimod, in the form of 3.75% Zyclara cream, was mostly effective in treating non-hypertrophic facial AKs following a week long application cycle. In our per protocol analysis, all patients demonstrated either complete or partial clearance of their facial AKs at week 8, as 37.5% of patients experienced

complete clearance and 62.5% experienced partial clearance. The results at month 12 differed, with 14.3% of patients experiencing complete clearance, 71.4% experiencing partial clearance, and 14.3% having no clearance. The patient experiencing complete clearance at month 12 was not among the group who demonstrated complete clearance at week 8, suggesting the potential for late responsiveness to the treatment.

In these results, one of the patients was lost to follow-up by month 12. This individual was included in the response rate at week 8 when having demonstrated partial clearance. During the next patient visit at month 6, this individual showed an increase in the number of facial AK lesions.

Calculation of disease free time could not be completed due to the study's small sample size and having only three patients demonstrating complete clearance at week 8. These patients were disease free at both week 4 and week 8, but two of these patients had AK recurrence by month 6. The other patient with this initial complete clearance was lost to follow-up by month 6; however, this patient returned at month 12 with recurrence. Consequently, disease free time could not be reliably measured.

Ease of treatment use was also determined. On the subjective patient rating scale from 1-10 (1 very easy, 10 very hard), all patients reported very easy to easy use. Most patients (70%) reported the use of Zyclara to be very easy, responding with a 1 on the rating scale. The remaining patients rated the treatment as a 3 (20%) or a 4 (10%) on the scale. This reflects the convenience of Zyclara use and strengthens its potential success to treat facial AKs.

Adverse events were assessed by the study dermatologist and through patient reports following treatment with Zyclara. On day 7, all patients exhibited localized erythema and most experienced other general skin reactions with pruritus and edema being most common. Less than half of the individuals reported other adverse skin reactions of scaling crusted skin, excoriation, and burning. These side effects local to the site of application are consistent with cutaneous immune system stimulation and may even act as a clinical marker proving the mechanism of imiquimod to enhance immune response.18 Other adverse events reported occurred in ≤ 2 patients and were not of serious concern. All adverse events, including the localized erythema seen in every patient, were resolved by day 14. As well, none of the patients failed to complete the full duration of treatment due to side effects. Therefore, it can be established that the treatment was well tolerated.

The local immune response following Zyclara application indicates its efficacy as an immune response modifier. Imiquimod products have been shown to stimulate the immune system by activating antigen presenting cells, these being monocytes/macrophages and dendritic cells, that lead to cytokine production. This response may be mediated through toll-like receptor 7, which recognizes Pathogen Associated Molecular Patterns (PAMPs) and induces the transcription of multiple subtypes of pro-inflammatory cytokines. Cytokines can then support the cell mediated immune response, helping to trigger lymphocyte influx into the epidermis and upregulating apoptotic signalling pathways [18,19]. The activation of langerhans cells has also been found to be enhanced with imiquimod application, allowing for increased recognition of antigens expressed by damaged cells [20]. This overall immune response stimulation is an adequate therapeutic technique to treat AKs because AK pathogenesis relates to immune response suppression from chronic UV light exposure. Accordingly, imiquimod use can lead to clearance of AK lesions and fewer recurrences.

As there is a possibility for AK lesions to develop into invasive SCC, the importance of AK treatment is evident. There is no certain way to determine if an AK lesion will progress into SCC, therefore early treatment can help avoid this invasive transformation [21]. It can be postulated that early AK intervention with imiquimod can drastically lower long-term negative effects associated with SCC development.

Conclusion

The results from this study indicate that 3.75% Zyclara cream is a safe and well tolerated topical treatment for AK, and is an effective therapy for partial AK clearance. As well, the shortened treatment duration of Zyclara of one week has shown to limit adverse events.

Additional research is needed to examine the long-term efficacy and exact mechanism of Zyclara. It is recommended that future studies use randomized comparator groups and a larger study population to increase generalizability of these results. However, these findings suggest that daily, week-long Zyclara application is an easy-to-use treatment that can reduce the risk of AK recurrence with minimal adverse side effects.

Limitations

Despite the results of this study extending upon the information on the clinical use of imiquimod in treating AKs, its limitations need to be considered. As this was a non-randomized study, the impact of potential bias was heightened. The evaluation of the clinical effects of the zyclara cream could have been overestimated, especially considering the assumed pharmacodynamic effect of this treatment may have influenced the investigator's assessment. In addition, the lack of a comparator group can lead to extraneous variables having an increased effect on study results. Finally, due to the study's small sample size and having no long-term follow-up data past month 12, there is decreased accuracy in the reported AK recurrence rate.

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Conflicts of Interest

All authors declare there are no conflicts of interest associated with this publication.

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