ORIGINAL RESEARCH

Do Second-Time Users of Topical Imiquimod have a More Rapid Onset of Clinical Response?

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ABSTRACT

Introduction: Topical imiquimod is commonly used in dermatology for treatment of actinic keratoses (AK). Prior studies in humans and mice have suggested the potential for immune recall with imiquimod based on higher degrees of AK clearance and activation of memory γδ T-cells in a mouse model. Anecdotal reports suggest a more rapid time-to-onset of clinical response with second time use of imiquimod. However, the potential for immune recall demonstrated by time-to-onset of clinical response has not been formally investigated.

Objective: The primary objective of this study was to determine if there is a difference in time-to-onset of clinical response between naïve and prior users of topical imiquimod for the treatment of actinic keratoses.

Methods: A total of 92 patients were treated with 5% imiquimod cream for actinic keratoses of the head and neck. Patients were instructed to apply 5% imiquimod cream to the affected areas once daily until reaching a therapeutic endpoint of crusting/scabbing. The primary endpoints in the study were time (days) to onset of erythema and time to onset of crusting/scabbing. Results were self-reported.

Results: The average time (days) to onset of erythema was 5.48 ± 3.19 days in naïve users and 4.7 ± 2.91 days in prior users (p= 0.22). Average time to onset of crusting/scabbing was 9.2 ± 4.34 days in naïve users and 9.02 ± 3.65 days in prior users (p=0.35).

Conclusion: Our study revealed there is no difference in time-to-onset of erythema or scabbing/crusting with second-time use of imiquimod. While immune recall may be possible with use of imiquimod, the results of this study indicate that it may be independent of time-to-onset of clinical response.

INTRODUCTION

Topical imiquimod is a commonly used therapy in dermatology, approved for treatment of actinic keratoses (AK), genital warts, and superficial basal cell carcinoma.[1] It is also frequently used off-label for treatment of select squamous cell carcinoma in-situ, melanoma in-situ, and a variety of other dermatologic conditions.[2] Imiquimod was initially thought to exert antiviral and antitumoral effects via selective agonism of toll-like receptor 7 (TLR7). Recent studies have revealed that its mechanism of action is more complex. Imiquimod stimulates innate and adaptive immunity not only via TLR7, but also through toll-like receptor 8 (TLR8), the nuclear factor kappa B (NF-κB) pathway, the hedgehog pathway (via adenylate cyclase), and the opioid growth factor receptor (OGFR) (Figure 1).[3,4]

Many AK treatment protocols utilizing imiquimod dictate several courses of therapy separated by rest periods. In addition, some patients will use a second course of imiquimod months or even years after their initial course. Patients and physicians have anecdotally reported that time-to-onset of clinical response is shorter in patients who have previously used imiquimod, proposing the generation of immune recall with use of the medication.

The potential for immune recall with imiquimod has been previously suggested based on studies showing higher rates of sustained field clearance.[2] One study by Krawtchenko et al reported that 5% imiquimod cream produced significantly greater sustained total field clearance of AK at 12-months post treatment when compared to 5-FU and cryotherapy.[5] In a mouse model, Hartwig et al showed imiquimod-induced clonal expansion of memory γδ T-cells, which persisted in both treated and untreated dermis long after initial treatment (6). Second time use of imiquimod in these mice resulted in a robust and exaggerated inflammatory response.

In this report, we present observations that arose from a quality improvement (QI) project initially designed to improve documentation of treatment response time in patients with actinic keratoses. Our findings shed light onto whether the aforementioned phenomenon can be detected clinically in patients by comparing time-to-onset of clinical response in naïve and prior users of imiquimod for treatment of actinic keratoses.

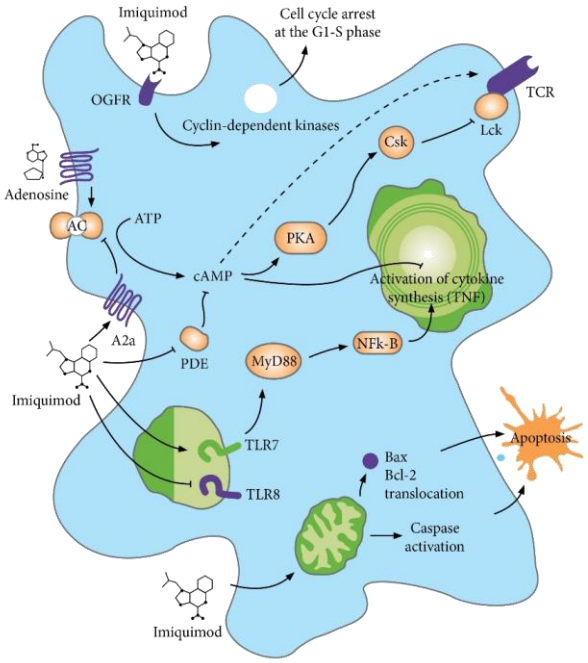

Figure 1. Imiquimod Mechanism of Action.
Imiquimod acts via agonism of toll-like receptor 7 (TLR7) and the nuclear factor kappa-B (NFκ-B) pathway, antagonism of toll-like receptor 8 (TLR8), the A2a receptor via adenylate cyclase (a precursor in the downstream hedgehog pathway), and the opioid growth factor receptor (OGFR). Adapted from Bozrova et al 2013.

METHODS

As part of a QI initiative performed in a private practice setting, a protocol of data collection was put in place for patients treated with 5% imiquimod cream for actinic keratoses of the head and neck. The goal of this data collection initiative was to determine factors leading to quicker onset of action and better outcomes that could be applied to future QI cycles. A total of 92 patients were included in this initiative. As per our standard protocol, patients were instructed to apply 5% imiquimod cream to the affected areas once daily until reaching a therapeutic endpoint of crusting/scabbing. Patients received extensive instruction on medication use, supplemented with clinical photos of the desired endpoints of erythema and crusting/scabbing. The primary data points collected were time (days) to onset of erythema and time to onset of crusting/scabbing. Results were self-reported, and all patients were evaluated in clinic at follow up in 14 days. Patients were asked to send a clinical photo for

telemedicine review or to come to the clinic for evaluation if in doubt of whether they had reached the desired endpoint.

When analyzing the results for QI purposes, an interesting observation regarding onset of clinical response in those who had been previously treated with imiquimod versus those who were imiquimod-naïve arose, and further analysis (stratifying results by these two treatment groups) was performed to investigate these findings more thoroughly.

RESULTS

Out of the 92 patients who took part in this project, there were 41 naïve users and 51 prior users of imiquimod. All patients reported adherence to the specified treatment regimen, and no unexpected adverse events were noted. The average time (days) to onset of erythema was 5.48 ± 3.19 days in naïve users and 4.7 ± 2.91 days in prior users (p= 0.22). Average time to onset of crusting/scabbing was 9.2 ± 4.34 days in naïve users and 9.02 ± 3.65 days in prior users (p=0.35) (Figure 2). There was no statistically significant difference between the two groups.

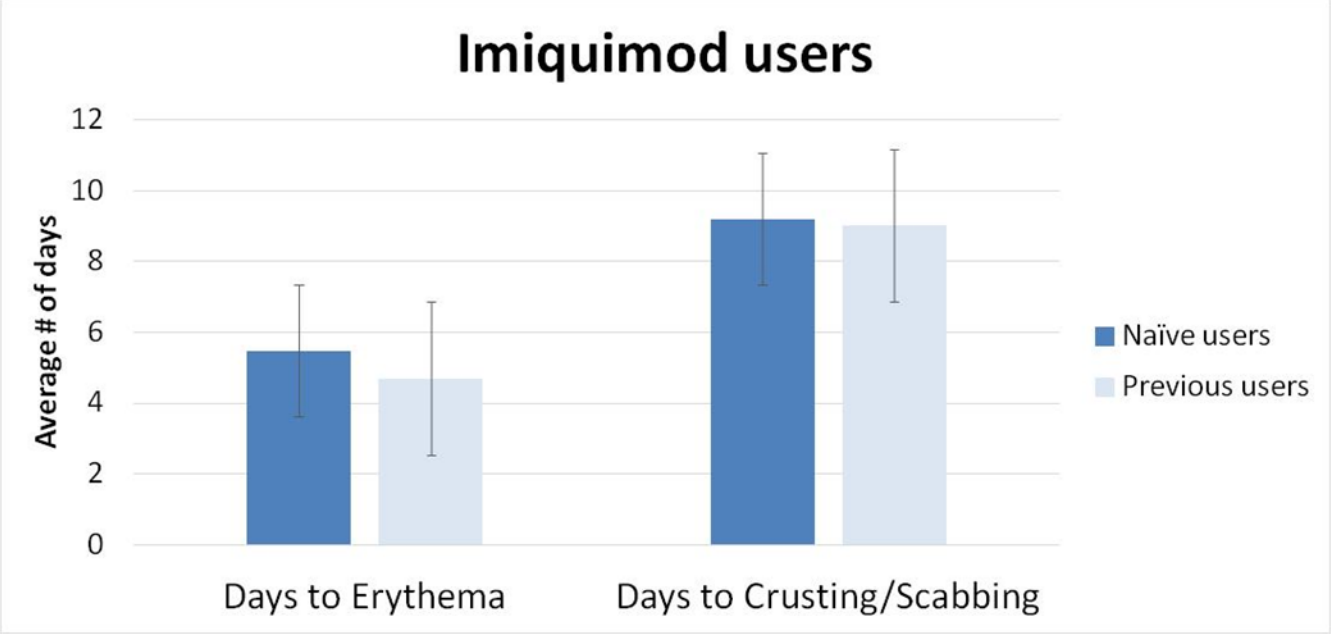

Figure 2. Results.
The average time (days) to onset of erythema was 5.48 ± 3.19 in naïve users and 4.7 ± 2.91 in prior users (p= 0.22). Average time (days) to onset of crusting/scabbing was 9.2 ± 4.34 in naïve users and 9.02 ± 3.65 in prior users (p=0.35).

DISCUSSION

Imiquimod has been shown to act via a variety of complex mechanisms involving both innate and adaptive immunity. Prior studies suggestive of higher sustained field clearance of AK with imiquimod, mouse studies showing activation of memory γδ T-cells, and numerous anecdotal reports from patients and physicians of faster onset of clinical response with second time use suggest the potential for immune recall. Our study revealed there is no difference in time-to-onset of erythema or scabbing/crusting with second-time use of imiquimod. While immune recall may be possible with use of imiquimod, the results of this study indicate that it may be independent of time-to-onset of clinical response.

Knowledge of time-to-onset of clinical response with use of imiquimod has significant clinical implications. It allows practitioners to appropriately set patient expectations for length of treatment course with initial and subsequent use. Practitioners can also anticipate that the same quantity of medication may be required for each treatment course. While no difference in time-to-onset of clinical response was seen in this study, there is still evidence for higher sustained clearance of AK with use of imiquimod. With changing payment models and the potential for bundled reimbursement for clearance of AK, knowledge of which therapies achieve and sustain the highest degree of clearance may have financial implications in the future.[7]

Limitations of the study include the small sample size and the single clinical setting, in addition to the fact that our observations spawned from a QI project. Moreover, only actinic keratoses were studied, and the self-reported nature of the primary outcomes is subject to recall bias. There is also potential for confounding factors given the observational nature of the study.

Conflict of Interest Disclosures: None

Funding: None

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