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Published in:
Journal of Dermatological Treatment

DOI:
10.1080/09546634.2021.1917758

Publication date:
2022

Document version:
Final published version

Document license:
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Citation for published version (APA):
Emmerich, V. K., Cull, D., Kelly, K. A., & Feldman, S. R. (2022). Patient assessment of 5-fluorouracil and imiquimod for the treatment of actinic keratoses: a retrospective study of real-world effectiveness. Journal of Dermatological Treatment, 33(4), 2075-2078. https://doi.org/10.1080/09546634.2021.1917758

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Download date: 01. Nov. 2023
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To cite this article: Veronica K. Emmerich, Deborah Cull, Katherine A. Kelly & Steven R. Feldman (2021): Patient assessment of 5-fluorouracil and imiquimod for the treatment of actinic keratoses: a retrospective study of real-world effectiveness, Journal of Dermatological Treatment, DOI: 10.1080/09546634.2021.1917758

To link to this article: https://doi.org/10.1080/09546634.2021.1917758

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Published online: 05 May 2021.

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Patient assessment of 5-fluorouracil and imiquimod for the treatment of actinic keratoses: a retrospective study of real-world effectiveness

Veronica K. Emmerich, Deborah Culla, Katherine A. Kelly and Steven R. Feldman

ABSTRACT
Background: Despite the superior efficacy of topical therapies for the treatment of actinic keratoses in clinical trials, cryosurgery remains a frequent treatment modality in clinical practice. Little is known about patients’ experience of real-world use of topical therapy.

Objective: To determine the real-world effectiveness and tolerability of 5-fluorouracil and imiquimod in the treatment of actinic keratoses.

Methods: A phone survey and chart review was conducted among 51 patients prescribed 5-fluorouracil (N = 27) or imiquimod (N = 24) for actinic keratoses.

Results: Six patients (22%) in the 5-fluorouracil group and five patients (21%) in the imiquimod group reported severe local skin reactions, and three patients in both groups (11% and 13%, respectively) were unwilling to use the respective topical therapies again. Patients in the 5-fluorouracil group had, on average, 3.3 fewer cryosurgery spot treatments following topical treatment. Patients in the imiquimod group averaged 2.0 fewer spot treatments.

Limitations: While this study provides information on real-world experiences, patients’ responses were limited by the ability to recall treatment and potential adverse effects.

Conclusion: High rates of skin reactions, prolonged discomfort, and the continued need for procedural treatments may make patients less willing to use topical 5-fluorouracil or imiquimod for actinic keratoses.

Introduction
Actinic keratoses (AK) are rough, erythematous plaques with potential for malignant transformation and negative cosmetic consequences (1,2); they result from chronic sun exposure and are associated with fair skin and increasing age. Treatment of AK depends on the number of lesions present; individual lesions are frequently targeted with procedural therapies, such as cryosurgery and curettage, while field treatments are medical options that target widespread or numerous lesions. Topical field therapies include 5-fluorouracil (5-FU), imiquimod, ingenol mebutate, and tirbanibulin (3,4). These molecules operate via a variety of mechanisms—including disruption of DNA synthesis, immune system stimulation, induction of a cytotoxic response, or inhibition of microtubules—that preferentially target dysplastic and rapidly dividing cells (4–7). These molecules preferentially target dysplastic and rapidly dividing cells and induce an inflammatory response or apoptosis. This makes them effective therapies for tissues subjected to field cancerization such as photodamaged skin, which may show histologic changes before AKs are clinically apparent. However, despite the efficacy of 5-FU and imiquimod for complete clearance of AKs, cryosurgery remains a frequently used treatment modality even in the setting of multiple AKs (8).

In clinical studies of topical AK treatments, patients are typically highly adherent, which results in high therapeutic efficacy (9). However, little is known about patients’ experience of these medications in typical clinical practice settings. The objective of our study was to characterize the real-world effectiveness and tolerability of 5-FU and imiquimod via a phone survey and chart review of patients prescribed either for the treatment of AK.

Materials and methods
Patient identification and enrollment
Patients prescribed 5-FU or imiquimod for the treatment of AK between January 2017 and January 2019 were identified via i2b2 query. Patients were identified from a single site, Wake Forest Baptist Health. From this list of potential participants, patients were contacted via phone to ascertain their willingness to participate in the study. A random number generator was used to select patients to be contacted; if the patient was willing to participate, a phone survey was conducted (Table 1), and the patient’s medical records were reviewed.

Basic demographic data and medication history were recorded, as well as a history of non-melanoma skin cancers (NMSCs) and dermatologic procedures performed one year
before and one year after initiation of topical treatment. The number of spot treatments for AK were recorded; in cases where more than 15 AK were treated but a specific number was not noted, 16 spot treatments were counted. The study aimed to recruit up to 30 patients treated with 5-FU and up to 30 patients treated with imiquimod for a total enrollment of up to 60 patients. There were no exclusion criteria.

Analyses

Patient demographics, survey responses, and medical histories were analyzed with descriptive statistics.

Results

One thousand forty-six patients were identified in the group prescribed 5-FU, and 71 patients were identified in the imiquimod group. Of these, 27 patients were recruited from the 5-FU group and 24 patients from the imiquimod group.

Demographic data and survey results

Both groups were demographically similar (Table 2). The average age in the 5-FU group was 73.6 years (SD 7.5), and the average age in the imiquimod group was 69.8 years (SD 10.8). All participants were white.

The survey format allowed patients to expand upon their answers, resulting in some qualitative data in addition to quantitative results (Table 2). In the 5-FU group, two patients reported stopping treatment due to the severity of local skin reactions. Both of these patients stated they would not use 5-FU again. One patient with mild local skin reaction was unwilling to use 5-FU again due to difficulty and inconvenience of use, and another patient was only willing to use 5-FU again if they did not have to leave the house for a month.

In the imiquimod group, three patients reported adverse effects other than skin reactions. One reported fever and night sweats, one reported blurry vision, and one reported fatigue. Two of these patients expressed willingness to use imiquimod again. Of the three patients unwilling to use imiquimod again, two reported that the medication did not successfully treat their AKs.

Chart review

In the 5-FU group, 22 patients were prescribed 5% 5-FU cream, 4 patients were prescribed 0.5% 5-FU cream, and one patient was prescribed both depending on the site of use. In the imiquimod group, all patients were prescribed 5% imiquimod cream.

The occurrence of dermatologic procedures and NMSCs one year before and after initiating 5-FU or imiquimod were recorded (Table 3). In the 5-FU group, patients received an average of 9.3 (SD 11.9) and 6.0 (SD 9.0) cryosurgery spot treatments before and after starting topical therapy, respectively. Patients were diagnosed with an average of 0.67 NMSCs both before (SD 0.92) and after (SD 1.6) 5-FU therapy.

| Table 1. Phone survey questionnaire. |
|------------------------------------|
| Our records indicate that between January 2017 and January 2019, you were prescribed a topical treatment for actinic keratoses and that you filled this prescription. |
| 1. Did you start using this treatment for your actinic keratosis(es)? |
| 2. If you started treatment, did you complete the treatment course as prescribed? |
| 3. Did you experience any irritation or local skin reactions as a result of this treatment? If so, how severe were these reactions? |
| 4. Did you experience any inconvenience or stress due to local skin reactions? |
| 5. Did you experience any other adverse effects as a result of treatment? |
| 6. Did the treatment affect your daily life activities, such as work and social engagements? |
| 7. If you completed the treatment course as prescribed, was it successful in treating your actinic keratosis(es)? |
| 8. If treatment was not successful, did you require further therapy (for example, cryosurgery) for resolution of your actinic keratosis(es)? |
| 9. If treatment was not successful, did you switch to a different topical medication? If so, what medication did you switch to? |
| 10. Would you use 5-FU or imiquimod again for treatment of actinic keratosis(es)? |

| Table 2. Characteristics and survey responses of study participants. |
|---------------------------------------------------------------|
|                                                              |
|                                                              |
| 5-Fluorouracil (N = 27)                                      |
| Imiquimod (N = 24)                                           |
| Gender                                                       |
| Male                                                         |
| 21               78%                                           |
| Female                                                       |
| 6                22%                                           |
| Age                                                          |
| 50–59                                                       |
| 1                3.7%                                          |
| 60–69                                                       |
| 5                18%                                           |
| 70–79                                                       |
| 18               67%                                           |
| 80–89                                                       |
| 3                11%                                           |
| 90+                                                         |
| 0                0%                                            |
| Completed treatment                                         |
| Yes                                                          |
| 21               78%                                           |
| No                                                           |
| 6                22%                                           |
| Any reaction                                                |
| Yes                                                          |
| 19               70%                                           |
| No                                                           |
| 8                30%                                           |
| Specific reactions                                          |
| Redness                                                     |
| 15               56%                                           |
| Initiation                                                  |
| 9                33%                                           |
| Itch                                                        |
| 0                0%                                            |
| Photosensitivity                                            |
| 2                7.4%                                          |
| Scaling                                                     |
| 2                7.4%                                          |
| Blistering                                                  |
| 1                3.7%                                          |
| Swelling                                                    |
| 0                0%                                            |
| Reaction severity                                           |
| Mild                                                        |
| 12               44%                                           |
| Moderate                                                   |
| 1                3.7%                                          |
| Severe                                                      |
| 6                22%                                           |
| Inconvenience/Stress                                        |
| Yes                                                         |
| 3                11%                                           |
| No                                                          |
| 24               89%                                           |
| Affected work/Social life                                   |
| Yes                                                         |
| 4                15%                                           |
| No                                                          |
| 23               85%                                           |
| Treatment successful                                        |
| Yes                                                         |
| 22               81%                                           |
| No                                                          |
| 4                15%                                           |
| Unsure                                                      |
| 1                3.7%                                          |
| Would use again                                             |
| Yes                                                         |
| 23               85%                                           |
| No                                                          |
| 3                11%                                           |
| Unsure                                                      |
| 1                3.7%                                          |

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In the imiquimod group, patients received an average of 5.4 (SD 8.4) and 3.4 (SD 7.7) cryosurgery spot treatments before and after starting topical therapy, respectively. Patients were diagnosed with an average of 1.1 (SD 1.7) NMSCs before and 0.42 (SD 0.78) NMSCs after imiquimod therapy.

**Discussion**

Although 5-fluorouracil and imiquimod did reduce the overall number of procedural cryosurgery treatments for AK, there was considerable variation among individuals, and many patients continued to require procedural spot treatments. It is difficult to draw conclusions from the number of NMSCs diagnosed in either group; although the 5-FU group saw a greater reduction in cryosurgery treatments than the imiquimod group, only the imiquimod group saw a reduction in NMSCs after treatment. Regardless of treatment outcomes, many patients were dissatisfied with the prolonged discomfort and exuberance of local skin reactions. For some patients, the higher risk of treatment failure and AK recurrence with cryosurgery may be worth avoiding the discomfort of topical 5-FU or imiquimod therapies.

Medication efficacy in clinical trials is generally greater than in real-world use. Participation in a clinical trial enhances adherence to therapy, while the presence of side effects decreases adherence to therapy (10,11). Additionally, adherence to topical therapies is notoriously poor compared with oral therapies (12). Therefore, our study—examining the real-world use of a topical treatment with a high rate of unpleasant side effects—likely captures a clinical picture quite different from that of a clinical trial.

Our study has some advantages compared with a prospective clinical trial. While a prospective trial would have the advantages of a standardized protocol (duration, daily applications, size of the treated area) and objective measurement of the degree of inflammation, an advantage of our study is that it is informative of what patients’ experiences are in real-life clinical practice. However, this approach does have limitations. First, some patients were contacted who did not recall being prescribed either medication. This may reflect selection bias in the study, as patients who tolerate topical therapies may be more likely to continue using them and to subsequently recall their use; alternatively, patients who experience severe reactions or adverse effects due to a medication may be more likely to recall its use. Second, the survey was administered via phone and therefore answers were free response; responses—particularly to questions about symptoms and whether treatment was successful—were limited to what participants recalled about treatment and subsequent therapies. Next, far more potential participants were identified in the 5-FU group than the imiquimod group; this may be due to institutional bias, prescribing patterns, or a difference between patient groups. Also, our assessments of skin cancers were based on available medical records; an in-person evaluation might have detected additional cutaneous malignancies not yet diagnosed or documented. Finally, this was a single-site study with a homogenous and small sample size; therefore, it may not be generalizable to other populations.

The qualitative and quantitative data collected in our study suggest that novel or combination therapies for AK, particularly those with shorter duration and greater tolerability, would be welcome (13). For example, a one-week course of low-dose (0.5%) 5-fluorouracil followed by cryosurgery is more effective than cryosurgery alone in long-term clearance of AK lesions (14). The combination of a lower-dose medication followed by an office visit decreases the likelihood of side effects while increasing patient accountability to the treatment plan; however, this approach increases the number of office visits, which may be burdensome to patients. Alternatively, patient-centered interventions—such as tailoring communication and treatment to specific patient ‘profiles’—may improve satisfaction with and adherence to therapy. Providing efficacy and safety data to patients with high medical literacy or recommending healing creams for patients concerned with cosmesis, for example, may improve both communication and the patient-physician relationship (15,16). However, while a strong patient-physician relationship certainly helps, it is unlikely to ensure adherence against intolerable adverse effects. Ultimately, the best outcomes in treatment of AK lesions are likely to be achieved through a patient-centered approach in combination with more tolerable topical therapies.

**Disclosure statement**

Dr. Steven Feldman has received research, speaking and/or consulting support from a variety of companies including Galderma, GSK/Stiefel, Almirall, Leo Pharma, Boehringer Ingelheim, Mylan, Celgene, Pfizer, Valeant, Abbvie, Samsung, Janssen, Lilly, Menlo, Merck, Novartis, Regeneron, Sanofi, Novan, Quirient, National Biological Corporation, Caremark, Advance Medical, Sun Pharma, Suncare Research, Informa, UpToDate and National Psoriasis Foundation. He is founder and majority owner of www.DrScore.com and founder and part owner of Causa Research, a company dedicated to enhancing patients’ adherence to treatment. Veronica Emmerich, Deborah Cull, and Katherine Kelly have no conflicts to disclose.

**Funding**

This research was supported with funding from Almirall, LLC.

**References**

1. Siegel JA, Korgavkar K, Weinstock MA. Current perspective on actinic keratosis: a review. Br J Dermatol. 2017;177(2):350–358.

**Table 3.** Dermatological procedures and non-melanoma skin cancers one year before and after initiation of therapy.

|                      | 5-Fluorouracil | Imiquimod |
|----------------------|----------------|-----------|
|                      | N              | N         |
| Procedures before treatment |                |           |
| Cryosurgery          | 251 (94.5)     | 129 (84.4)|
| Excision             | 7 (2.6)        | 3 (2.0)   |
| MMS                  | 4 (1.4)        | 1 (0.7)   |
| Other                | 2 (0.6)        | 6 (4.1)   |
| Procedures after treatment |            |           |
| Cryosurgery          | 162 (100)      | 81 (100)  |
| Excision             | 1 (0.6)        | 0 (0.0)   |
| MMS                  | 4 (2.4)        | 2 (2.5)   |
| Other                | 4 (2.4)        | 4 (4.9)   |
| NMSCs before treatment | 18 (100)       | 26 (100)  |
| NMSCs after treatment | 18 (100)       | 10 (100)  |

NMSC: non-melanoma skin cancer; MMS: Mohs micrographic surgery.
2. de Oliveira ECV, da Motta VRV, Pantoja PC, et al. Actinic keratosis – review for clinical practice. Int J Dermatol. 2019;58(4):400–407.
3. Hashim PW, Chen T, Rigel D, et al. Actinic keratosis: current therapies and insights into new treatments. J Drugs Dermatol. 2019;18(5):s161–s166.
4. Blauvelt A, Kempers S, Lain E, et al. Phase 3 trials of tirbanibulin ointment for actinic keratosis. N Engl J Med. 2021;384(6):512–520.
5. Casale J, Crane JS. Fluorouracil. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK549808/.
6. Hanna E, Abadi R, Abbas O. Imiquimod in dermatology: an overview. Int J Dermatol. 2016;55(8):831–844.
7. Alchin DR. Ingenol mebutate: a succinct review of a succinct therapy. Dermatol Ther. 2014;4(2):157–164.
8. de Berker D, McGregor JM, Mohd Mustapa MF, et al. British Association of Dermatologists’ guidelines for the care of patients with actinic keratoses 2017. Br J Dermatol. 2017;176:20–43.
9. Yentzer B, Hick J, Williams L, et al. Adherence to a topical regimen of 5-fluorouracil, 0.5%, cream for the treatment of actinic keratoses. Arch Dermatol. 2009;145(2):203–205.
10. van Onzenoort HA, Menger FE, Neef C, et al. Participation in a clinical trial enhances adherence and persistence to treatment: a retrospective cohort study. Hypertension. 2011;58(4):573–578.
11. Snyder S, Crandell I, Davis SA, et al. Medical adherence to acne therapy: a systematic review. Am J Clin Dermatol. 2014;15(2):87–94.
12. Krejci-Manwaring J, McCarty MA, Camacho F, et al. Adherence with topical treatment is poor compared with adherence with oral agents: implications for effective clinical use of topical agents. J Am Acad Dermatol. 2006;54(5):S235–S236.
13. Grada A, Feldman SR, Bragazzi NL, et al. Patient-reported outcomes of topical therapies in actinic keratosis: a systematic review. Dermatol Ther. 2021;34:e14833.
14. Jorizzo J, Weiss J, Furst K, et al. Effect of a 1-week treatment with 0.5% topical fluorouracil on occurrence of actinic keratoses after cryosurgery: a randomized, vehicle-controlled clinical trial. Arch Dermatol. 2004;140(7):813–816.
15. Philipp-Dormston WG, Battistella M, Boussemart L, et al. Patient-centered management of actinic keratoses. Results of a multi-center clinical consensus analyzing non-melanoma skin cancer patient profiles and field-treatment strategies. J Dermatolog Treat. 2020;31(6):576–582.
16. Neri L, Peris K, Longo C, et al. Physician-patient communication and patient-reported outcomes in the actinic keratosis treatment adherence initiative (AK-TRAIN): a multicenter, prospective, real-life study of treatment satisfaction, quality of life and adherence to topical field-directed therapy for the treatment of actinic keratosis in Italy. J Eur Acad Dermatol Venereol. 2019;33(1):93–107.