

Randomized Trial of Four Treatment Approaches for Actinic Keratosis

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ORIGINAL ARTICLE

Randomized Trial of Four Treatment Approaches for Actinic Keratosis

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ABSTRACT

BACKGROUND

Actinic keratosis is the most frequent premalignant skin disease in the white population. In current guidelines, no clear recommendations are made about which treatment is preferred.

METHODS

We investigated the effectiveness of four frequently used field-directed treatments (for multiple lesions in a continuous area). Patients with a clinical diagnosis of five or more actinic keratosis lesions on the head, involving one continuous area of 25 to 100 cm², were enrolled at four Dutch hospitals. Patients were randomly assigned to treatment with 5% fluorouracil cream, 5% imiquimod cream, methyl aminolevulinate photodynamic therapy (MAL-PDT), or 0.015% ingenol mebutate gel. The primary outcome was the proportion of patients with a reduction of 75% or more in the number of actinic keratosis lesions from baseline to 12 months after the end of treatment. Both a modified intention-to-treat analysis and a per-protocol analysis were performed.

RESULTS

A total of 624 patients were included from November 2014 through March 2017. At 12 months after the end of treatment, the cumulative probability of remaining free from treatment failure was significantly higher among patients who received fluorouracil (74.7%; 95% confidence interval [CI], 66.8 to 81.0) than among those who received imiquimod (53.9%; 95% CI, 45.4 to 61.6), MAL-PDT (37.7%; 95% CI, 30.0 to 45.3), or ingenol mebutate (28.9%; 95% CI, 21.8 to 36.3). As compared with fluorouracil, the hazard ratio for treatment failure was 2.03 (95% CI, 1.36 to 3.04) with imiquimod, 2.73 (95% CI, 1.87 to 3.99) with MAL-PDT, and 3.33 (95% CI, 2.29 to 4.85) with ingenol mebutate ($P \leq 0.001$ for all comparisons). No unexpected toxic effects were documented.

CONCLUSIONS

At 12 months after the end of treatment in patients with multiple actinic keratosis lesions on the head, 5% fluorouracil cream was the most effective of four field-directed treatments. (Funded by the Netherlands Organization for Health Research and Development; ClinicalTrials.gov number, NCT02281682.)

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ACTINIC KERATOSIS IS THE MOST FREQUENT premalignant skin disease in the white population and is caused by exposure to ultraviolet radiation. With a prevalence of 37.5% among whites 50 years of age or older, actinic keratosis is one of the most frequent reasons for patients to visit a dermatologist.¹⁻³ If left untreated, actinic keratosis may develop into squamous-cell carcinoma.^{4,5} However, no definable clinical characteristics distinguish which actinic keratosis lesions pose a risk and what proportion of actinic keratosis lesions will progress into a carcinoma. Percentages that have been reported in studies range from 0.025 to 16% per actinic keratosis lesion per year.⁶⁻⁹

The recurrence rate after treatment is high, often leading to repetitive treatments, although research suggests that the effect of fluorouracil (also called 5-fluorouracil) on actinic keratosis reduction can last for years.^{10,11} Solitary lesions can be treated with cryotherapy. However, patients with actinic keratosis often present with multiple lesions in one continuous area (so-called field change). Generally, field-directed therapies are preferred, because they not only are therapeutically effective for present actinic keratosis but also may have a prophylactic effect on the development of new lesions; in addition, they may prevent the development of squamous-cell carcinoma.¹¹⁻¹³

Current guidelines provide no clear recommendations about which treatment approach is preferred.¹⁴⁻¹⁷ Frequently prescribed and studied field-directed treatment approaches are fluorouracil cream, imiquimod cream, photodynamic therapy (PDT), and ingenol mebutate gel.

Currently, the choice of treatment often depends on the preferences of patients and their treating physicians. Evidence from randomized trials with direct comparison between treatments and with long-term follow-up is scarce.¹¹ The aim of this randomized, controlled trial was to compare treatment success at 12 months of 5% fluorouracil cream, 5% imiquimod cream, methyl aminolevulinate PDT (MAL-PDT), and 0.015% ingenol mebutate gel in patients with actinic keratosis lesions of any grade.

METHODS

TRIAL DESIGN AND POPULATION

This multicenter, single-blind, randomized trial was conducted at the dermatology departments

of four hospitals in the Netherlands. The trial was performed according to the principles of the Declaration of Helsinki, and the protocol (available with the full text of this article at NEJM.org) was approved by the local medical ethics committee. No commercial support was provided for the trial. The trial drugs were purchased as a part of routine care of the patients. No company had any role in the design of the trial, the collection or analysis of the data, or the writing of the manuscript. The authors vouch for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol.

Patients 18 years of age or older with a clinical diagnosis of five or more actinic keratosis lesions in one continuous area of skin measuring 25 to 100 cm² in the head and neck area were eligible for participation. Clinical diagnosis of actinic keratosis was made by the patient's own physician and verified by one of two investigators who assessed the end points without knowing the treatment assignment. In the case of a larger affected area, the investigator selected the area with the most pronounced lesions. All grades of actinic keratosis lesions (Olsen grades I to III, a three-point grading system based on thickness of hyperkeratosis, with higher grades indicating more severe lesions) were included. (For details on the Olsen scale, see the Supplementary Appendix, available at NEJM.org.) Patients were not eligible to participate if they had received any treatment for actinic keratosis (including cryotherapy) in the target area or had used systemic retinoids or systemic immunosuppressant drugs within 3 months before inclusion. Other reasons for exclusion were suspicion of cancer in the target area, porphyria, allergy to trial drugs, pregnancy or breast-feeding, or a personal history of a genetic skin-cancer disorder. All patients provided written informed consent before randomization.

RANDOMIZATION, TREATMENT, AND ASSESSMENTS

Patients were randomly assigned to one of four investigated treatments in a 1:1:1:1 ratio. Randomization lists that were based on minimization were computer generated with Alea software.¹⁸ Stratifying factors were treatment center and severity of actinic keratosis. An investigator who was aware of the treatment assignments (the second author) performed the randomization procedure. The second author was also responsible for the distribution of trial information and

medication and managed and recorded the adverse events as well as adherence. An investigator who was unaware of the treatment assignments (the first author) evaluated all trial end points, with the exception of adverse events and adherence during the baseline and follow-up visits.

The first author determined the number and extent of actinic keratosis lesions at the baseline visit and at 3 and 12 months after the end of treatment. All lesions were drawn with their exact location on a transparent sheet with the use of physical reference points as landmarks. The severity of each lesion was graded with the Olsen scale.¹⁹ Owing to the nature of the trial medication, patients were aware of the treatment assignments.

Details about the treatment protocols of fluorouracil, imiquimod, ingenol mebutate, and MAL-PDT are provided in the Supplementary Appendix. In all patients, superficial curettage of all actinic keratosis lesions was performed manually before every treatment or retreatment, and patients did not receive anesthesia.

The treatment strategy entailed a first treatment and allowed for a retreatment in case of insufficient treatment response, defined as a lesion response of less than 75% at the first follow-up visit (Fig. 1). For patients assigned to receive fluorouracil, ingenol mebutate, or MAL-PDT, initial treatment response was evaluated 3 months after the first treatment. For patients assigned to receive imiquimod, initial response was evaluated 1 month after the last treatment day, in accordance with the summary-of-product-characteristics guideline for imiquimod. All patients could receive a maximum of two courses of the assigned treatment. In case of less than 75% clearance of actinic keratosis 3 months after the final treatment, those patients were assessed as having treatment failure for the final analysis.

OUTCOMES

The primary outcome of this trial was the proportion of patients who remained free from treatment failure during 12 months of follow-up after the last treatment. Treatment failure was defined as a reduction of less than 75% in the number of actinic keratosis lesions counted at baseline and could occur at 3 months after the last treatment (initial failure) or at 12 months after initial successful treatment. Secondary outcomes were initial treatment success at 3 months after the last treatment (defined as $\geq 75\%$ reduc-

tion from baseline in the number of actinic keratosis lesions), adverse events, adherence, patient satisfaction with treatment, health-related quality of life, and cosmetic results. Details are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The sample size of this trial was based on the primary end point, lesion reduction of at least 75% at 12 months after the end of treatment. On the basis of previous studies, we estimated that 65% of patients would have lesion reduction of at least 75% at 12 months after the end of treatment.²⁰ To enable detection of an absolute difference of 15 percentage points between treatment groups with a power of 80% and an alpha level of 5%, a total of 140 patients were required per treatment group. To account for a potential loss to follow-up of 10%, a total of 624 (4×156) patients needed to be included.

The cumulative probability of remaining free from treatment failure at 12 months after the end of treatment was calculated with the use of Kaplan–Meier survival analysis of the observed outcome data at 3 and 12 months. Survival analysis was used to account for patients who were lost to follow-up and whose data were censored at the date of the last follow-up visit.

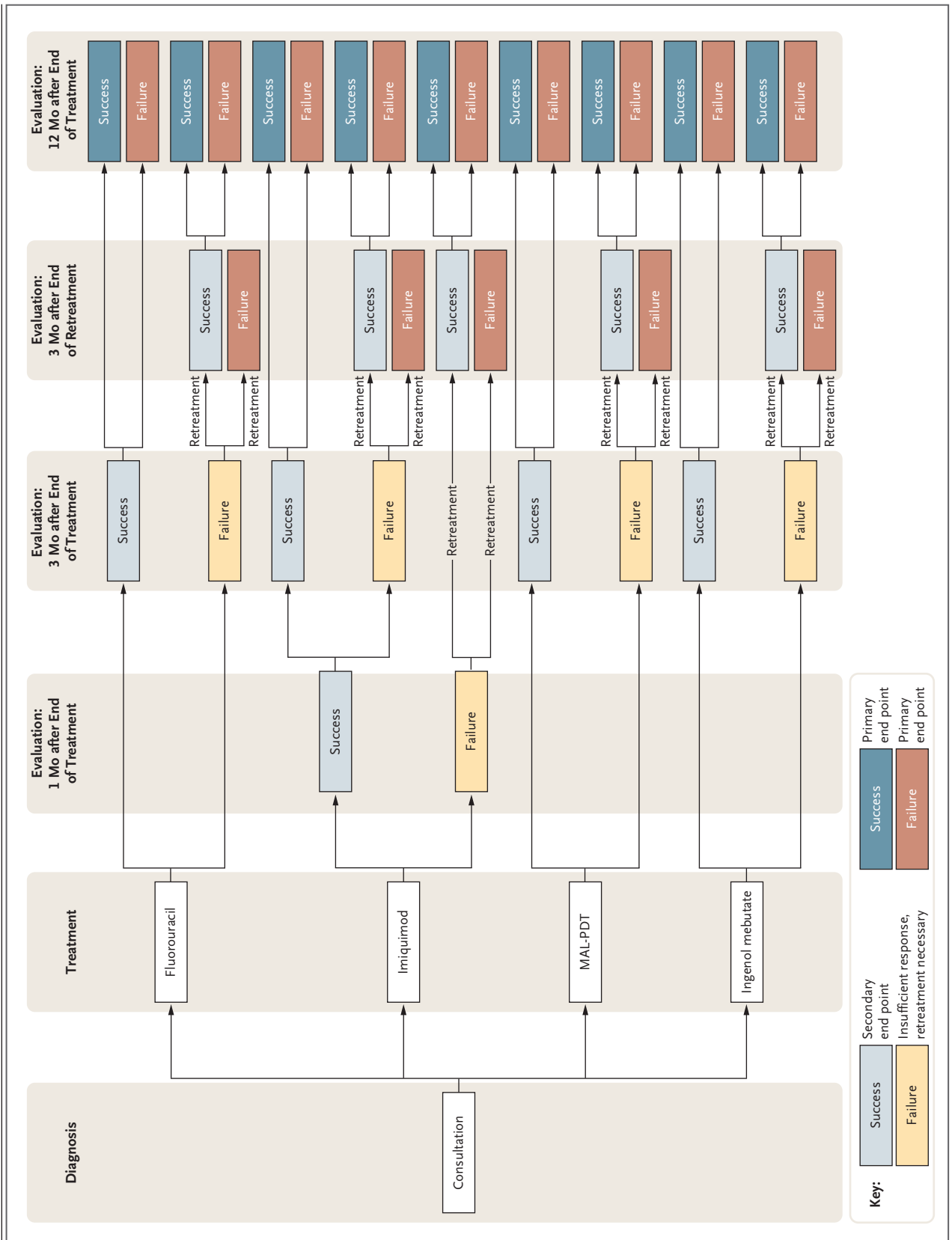
Cox regression analysis was used to calculate hazard ratios for treatment failure with 95% confidence intervals and P values; the treatment group with the highest rate of success was used as the reference group. Variables with dichotomous outcomes were compared between the treatment groups with the use of the chi-square test or Fisher's exact test for proportions. For continuous variables, between-group differences were compared with the use of analysis of variance (if normally distributed) or a nonparametric test for independent samples (if not normally distributed).

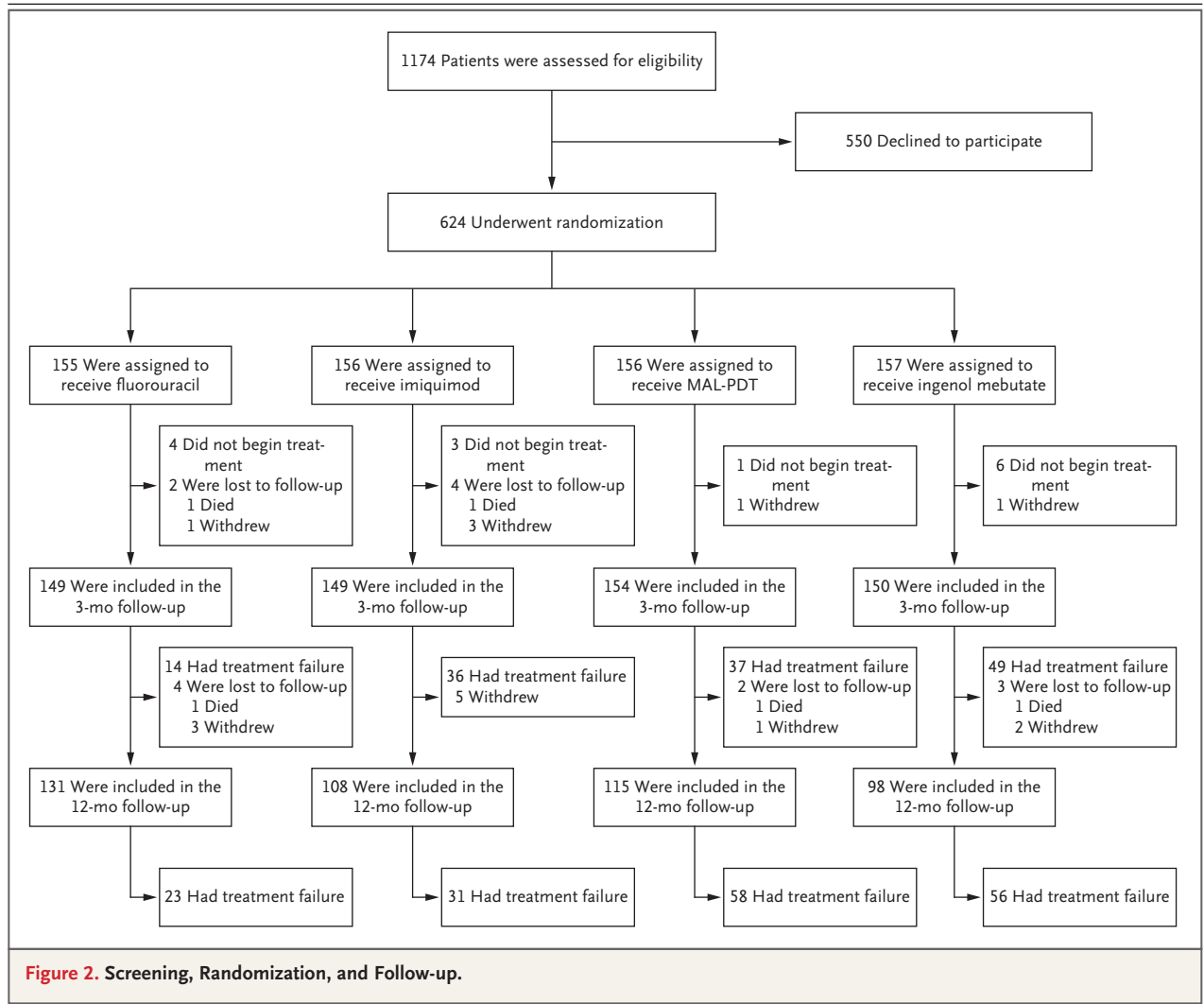
A Bonferroni adjustment was made for multiple comparisons with 0.008 ($0.05 \div 6$) as the alpha value, because there were six possible pairwise comparisons between treatment groups. Analyses were performed with the use of SPSS software, version 23.0 (IBM), and Stata software, version 14.0 (StataCorp).

RESULTS

TRIAL POPULATION

From November 2014 through March 2017, a total of 1174 patients were assessed for eligibility





(Fig. 2). Of those, 550 patients declined to participate for the following reasons: preference or disfavor regarding one or more of the studied treatments (197 patients), old age or coexisting conditions (113), disapproval to receive a treatment by randomization (88), decision of the patient not to have actinic keratosis treated (53), logistic reasons (24), concern about possible side effects (24), treatment costs (9), and preference for treatment in a different hospital (3). One patient died before informed consent could be ob-

tained, and 38 patients did not give a reason for declining to participate.

A total of 624 patients underwent randomization in four hospitals: Maastricht University Medical Center (247 patients), Catharina Hospital (176), VieCuri Medical Center (108), and Zuyderland Medical Center (93). A total of 155 patients were randomly assigned to fluorouracil, 156 to imiquimod, 156 to MAL-PDT, and 157 to ingenol mebutate. A total of 14 patients did not start treatment, and 8 patients were treated but did not attend the 3-month follow-up visit. Between 3 and 12 months, 14 patients were lost to follow-up (Fig. 2). Eight crossovers occurred before the assigned treatment was started, all because patients preferred a different therapy: 1 patient assigned to fluorouracil received MAL-PDT; 1 patient

Figure 1 (facing page). Schematic Presentation of the Treatment Strategies.

MAL-PDT denotes methyl aminolevulinate photodynamic therapy.

assigned to imiquimod received fluorouracil; 5 patients assigned to MAL-PDT received fluorouracil (3) or ingenol mebutate (2); and 1 patient assigned to ingenol mebutate received fluorouracil. No substantial imbalances in baseline characteristics were observed between treatment groups (Table 1). Although patients with actinic keratosis lesions on the neck were eligible for the trial, all the patients had lesions on the head only (vertex or face).

EFFECTIVENESS

A modified intention-to-treat analysis was based on 602 randomly assigned patients who started treatment and for whom data regarding the primary outcome were available. A total of 14 patients who declined treatment after randomization and 8 patients with early loss to follow-up were excluded (Table S1 in the Supplementary Appendix). In the modified intention-to-treat analysis, data were analyzed according to the treatment to which the patient was assigned by randomization.

The cumulative probability of treatment success for fluorouracil was 74.7% (95% confidence interval [CI], 66.8 to 81.0). For imiquimod, MAL-PDT, and ingenol mebutate, these percentages were 53.9% (95% CI, 45.4 to 61.6), 37.7% (95% CI, 30.0 to 45.3), and 28.9% (95% CI, 21.8 to 36.3), respectively, according to the modified intention-to-treat analysis (Table 2). A Bonferroni adjustment was made for multiple comparisons with the use of an alpha of 0.008 (0.05 ÷ 6), and the differences between fluorouracil cream and imiquimod, PDT, and ingenol mebutate were significant.

A per-protocol analysis was based on 555 patients who were treated and had full adherence to the treatment protocol. A total of 46 patients with initial treatment failure who declined retreatment were excluded. One other patient who requested retreatment with a different therapy was also excluded (Table S1 in the Supplementary Appendix). In the per-protocol analysis, data on the 8 patients who crossed over were analyzed according to the treatment they actually received. For all treatments, the probability of remaining free from treatment failure was slightly higher in the per-protocol population than in the modified intention-to-treat population, but the differences between fluorouracil cream and the other treatments remained significant (Table 2).

A treatment failure after one treatment cycle was observed in 14.8% of the patients (23 of 155) after fluorouracil therapy, 37.2% (58 of 156) after imiquimod therapy, 34.6% (54 of 156) after MAL-PDT, and 47.8% (75 of 157) after ingenol mebutate therapy. According to the trial protocol, a second treatment cycle was offered to all patients with treatment failure after one cycle. However, some patients declined a second treatment. This occurred more frequently in the imiquimod, MAL-PDT, and ingenol mebutate groups than in the fluorouracil group. Retreatment occurred in 19 of 23 patients (83%) with treatment failure after fluorouracil therapy. These percentages were lower in the other groups: 44 of 58 patients (76%) in the imiquimod group ($P=0.57$), 41 of 54 patients (76%) in the MAL-PDT group ($P=0.77$), and 60 of 75 patients (80%) in the ingenol mebutate group ($P=1.00$).

When we restricted the modified intention-to-treat analysis to patients with grade I or II actinic keratosis lesions, the percentages with treatment success were similar to those in the unrestricted analysis, and fluorouracil remained superior to the other treatments. For fluorouracil, the percentage was 75.3% (95% CI, 67.2 to 81.7). For imiquimod, PDT, and ingenol mebutate, the percentages were 52.6% (95% CI, 43.7 to 60.7), 38.7% (95% CI, 30.7 to 46.7), and 30.2% (95% CI, 22.6 to 38.1), respectively. The group with grade III actinic keratosis lesions was too small for separate analysis.

ADVERSE EVENTS

Data on adverse events (from completed patient diaries) were available for 135 patients who received fluorouracil, 121 who received imiquimod, 117 who received MAL-PDT, and 140 who received ingenol mebutate. There were no serious adverse events that were considered by the investigators and the medical ethics committee to be related to the trial treatment. Table 3 shows the percentages of patients who reported adverse events during treatment or the 2 weeks after the end of treatment. No patients discontinued the trial because of adverse events.

OTHER SECONDARY OUTCOMES

The percentage of patients with 100% adherence was higher in the ingenol mebutate group (98.7%) and the MAL-PDT group (96.8%) than in the fluorouracil group (88.7%) and the imiquimod group (88.2%). Patient satisfaction with treatment

Table 1. Baseline Characteristics of the Patients in the Modified Intention-to-Treat Population.*

Characteristic	Total (N = 624)	Fluorouracil (N = 155)	Imiquimod (N = 156)	MAL-PDT (N = 156)	Ingenol Mebutate (N = 157)
Sex — no. (%)					
Male	558 (89.4)	136 (87.7)	143 (91.7)	140 (89.7)	139 (88.5)
Female	66 (10.6)	19 (12.3)	13 (8.3)	16 (10.3)	18 (11.5)
Median age (range) — yr	73 (48–94)	74 (48–90)	73 (59–89)	73 (55–90)	72 (51–94)
Skin type — no. (%)†					
I	245 (39.3)	63 (40.6)	67 (42.9)	54 (34.6)	61 (38.9)
II	333 (53.4)	81 (52.3)	79 (50.6)	92 (59.0)	81 (51.6)
III	46 (7.4)	11 (7.1)	10 (6.4)	10 (6.4)	15 (9.6)
History of actinic keratosis — no. (%)					
Yes	487 (78.0)	121 (78.1)	129 (82.7)	115 (73.7)	122 (77.7)
No	137 (22.0)	34 (21.9)	27 (17.3)	41 (26.3)	35 (22.3)
History of nonmelanoma skin cancer — no. (%)‡					
Yes	353 (56.6)	90 (58.1)	82 (52.6)	86 (55.1)	95 (60.5)
No	271 (43.4)	65 (41.9)	74 (47.4)	70 (44.9)	62 (39.5)
Sun exposure — no. (%)§					
Mild	19 (3.0)	6 (3.9)	5 (3.2)	5 (3.2)	3 (1.9)
Moderate	283 (45.4)	69 (44.5)	73 (46.8)	72 (46.2)	69 (43.9)
Severe	322 (51.6)	80 (51.6)	78 (50.0)	79 (50.6)	85 (54.1)
History of immunosuppressive therapy >3 mo before inclusion — no. (%)¶					
Yes	84 (13.5)	18 (11.6)	25 (16.0)	19 (12.2)	22 (14.0)
No	540 (86.5)	137 (88.4)	131 (84.0)	137 (87.8)	135 (86.0)
Median treated area (range) — cm ²	81 (25–100)	80 (27–100)	86.5 (25–100)	81 (25–100)	78 (25–100)
Median no. of actinic keratosis lesions (range)	16 (5–48)	16 (5–48)	16.5 (5–37)	16 (5–38)	15 (5–40)
Severity of actinic keratosis — no. (%)					
Olsen grade I or II lesions	575 (92.1)	144 (92.9)	143 (91.7)	144 (92.3)	144 (91.7)
≥1 Lesion of Olsen grade III	49 (7.9)	11 (7.1)	13 (8.3)	12 (7.7)	13 (8.3)
Location of lesions — no. (%)					
Vertex	321 (51.4)	78 (50.3)	78 (50.0)	80 (51.3)	85 (54.1)
Face	303 (48.6)	77 (49.7)	78 (50.0)	76 (48.7)	72 (45.9)
Trial site — no. (%)**					
Maastricht	247 (39.6)	61 (39.4)	62 (39.7)	62 (39.7)	62 (39.5)
Eindhoven	176 (28.2)	43 (27.7)	44 (28.2)	44 (28.2)	45 (28.7)
Venlo	108 (17.3)	27 (17.4)	27 (17.3)	27 (17.3)	27 (17.2)
Heerlen	93 (14.9)	24 (15.5)	23 (14.7)	23 (14.7)	23 (14.6)

* There were no significant between-group differences in the characteristics listed here. Percentages may not total 100 because of rounding. MAL-PDT denotes methyl aminolevulinate photodynamic therapy.

† Skin type was graded according to Fitzpatrick's classification. Type I indicates always burns, never tans. Type II indicates burns easily, tans minimally. Type III indicates sometimes burns, slowly tans to light brown.

‡ Nonmelanoma skin cancer was defined as cutaneous melanoma or keratinocyte cancer.

§ Mild exposure was defined as no history of frequent sun exposure due to profession, tanning, or hobbies. Moderate exposure was defined as sun exposure only during leisure time or holidays. Severe exposure was defined as outdoor profession, frequent use of solar beds, a history of living in tropical areas, or participation in water sports.

¶ Immunosuppressive drugs included prednisolone, methotrexate, azathioprine, tacrolimus, or biologic agents.

|| The severity of each lesion was graded with the Olsen scale.¹⁹ This three-point grading system is based on thickness of hyperkeratosis, with higher grades indicating more severe lesions.

** The trial was conducted at four hospitals in the Netherlands: Maastricht University Medical Center (Maastricht), Catharina Hospital (Eindhoven), VieCuri Medical Center (Venlo), and Zuyderland Medical Center (Heerlen).

Table 2. Cumulative Probability of Treatment Success at 3 and 12 Months after the End of Treatment and Hazard Ratios for Treatment Failure.*

Variable	Treatment Success		Cumulative Probability of Remaining Free from Treatment Failure (95% CI)†		Hazard Ratio (95% CI)	P Value‡
	3 Mo after End of Treatment	12 Mo after End of Treatment	During 3 Mo after End of Treatment	During 12 Mo after End of Treatment		
	number/total	number (percent)	percent			
Modified intention-to-treat population						
Fluorouracil	135/149 (90.6)	108/131 (82.4)	90.6 (84.7–94.3)	74.7 (66.8–81.0)	1.00	
Imiquimod	113/149 (75.8)	76/107 (71.0)	75.8 (68.1–81.9)	53.9 (45.4–61.6)	2.03 (1.36–3.04)	0.001
MAL-PDT	117/154 (76.0)	57/115 (49.6)	76.0 (68.4–82.0)	37.7 (30.0–45.3)	2.73 (1.87–3.99)	<0.001
Ingenol mebutate	101/150 (67.3)	42/98 (42.9)	67.3 (59.2–74.2)	28.9 (21.8–36.3)	3.33 (2.29–4.85)	<0.001
Per-protocol population						
Fluorouracil	137/147 (93.2)	109/133 (82.0)	93.2 (87.7–96.3)	76.4 (68.6–82.5)	1.00	
Imiquimod	109/135 (80.7)	73/104 (70.2)	80.7 (73.0–86.5)	56.7 (47.7–64.7)	2.03 (1.33–3.10)	0.001
MAL-PDT	114/137 (83.2)	57/112 (50.9)	83.2 (75.8–88.5)	42.4 (33.9–50.5)	2.63 (1.76–3.94)	<0.001
Ingenol mebutate	102/136 (75.0)	42/99 (42.4)	75.0 (66.8–81.4)	31.8 (24.1–39.8)	3.33 (2.25–4.94)	<0.001

* Because the fluorouracil group had the highest rate of treatment success, it was used as the reference group, according to the statistical analysis plan. CI denotes confidence interval.

† Cumulative probabilities were based on Kaplan–Meier analysis.

‡ P values were based on Cox regression analysis.

DISCUSSION

This trial showed that 5% fluorouracil was significantly more effective than imiquimod, MAL-PDT, or ingenol mebutate at 12 months after the end of treatment for multiple actinic keratosis lesions in a continuous area. Findings from the modified intention-to-treat analysis and the per-protocol analysis were similar, which indicates the robustness of the results.

Although there is substantial literature about different field-directed and lesion-directed treatments, studies often lack head-to-head comparisons, differ substantially in choice of outcome measures, and are underpowered.^{14,21-23} Our randomized clinical trial compared four field-directed treatments with 12 months of follow-up.

Previously, two network meta-analyses have been published. One meta-analysis, by Vegter and Tolley,²⁴ indicated that aminolevulinic acid PDT (ALA-PDT) with the use of BF-200 ALA gel resulted in the highest probability (75.8%) of total clearance of actinic keratosis lesions, as compared with 0.5% fluorouracil (59.9%), 5% imiquimod (56.3%), and MAL-PDT (54.8%), with a follow-up of 3 to 12 months. But this meta-analysis did not include 5% fluorouracil, as was used in our trial. The other meta-analysis, by Gupta and Paquet,²⁵ suggested that 5% fluorouracil was the most effective treatment when complete clearance of all lesions was assessed. However, in the 2015 European Dermatology Forum guidelines, the majority of experts did not express a preference for any of the most commonly prescribed treatments.¹⁶ They agreed that 3.75% imiquimod, ALA-PDT, MAL-PDT, ingenol mebutate (0.015% or 0.050%), and 0.5% fluorouracil were equally effective in patients with multiple actinic keratosis lesions.¹⁶ However, there was less agreement on the effectiveness of 5% fluorouracil. In our trial, we used the most commonly prescribed dosing regimens of the therapies studied. Alternative regimens (e.g., dif-

ferent concentrations or duration of therapy) might result in differences in effectiveness between treatments.

An important gap in the current literature is that most studies assessing the effectiveness of field-directed treatments exclude grade III actinic keratosis lesions. In this trial, the population included patients with grade III actinic keratosis lesions; in this way, it is more representative of patients seen in daily practice. Exclusion of patients with grade III lesions was associated with slightly higher rates of success in the fluorouracil, MAL-PDT, and ingenol mebutate groups than the rates in the unrestricted analysis.

The reported adverse events in this trial are well-known treatment-related side effects that have been described in the corresponding summary of product characteristics. No treatment-related serious adverse events occurred. Overall, treatment with fluorouracil was not associated with a higher frequency of adverse events during and after treatment than the other treatments. High scores for pain and burning sensation were reported most often during MAL-PDT treatment. Pain can be an important reason for a patient to decline further treatment. In our trial, only 3.2% of the patients (5 of 155) in the MAL-PDT group did not complete the entire treatment owing to pain, but the proportion of patients who would undergo this treatment again and would recommend it to others was lower than for the other treatments, which indicates that pain may have influenced patient satisfaction with PDT. Satisfaction with treatment and improvement in health-related quality of life at 12 months after the end of treatment were highest in the fluorouracil group. This may be explained in part by the fact that fluorouracil was the most effective treatment. However, the high proportion of patients willing to undergo retreatment after initial treatment failure also suggests that patients treated with fluorouracil may have had less inconvenience and discomfort than those treated with imiquimod, MAL-PDT, or ingenol mebutate, for which the proportion of patients who declined retreatment were higher.

Dermatologists and primary health care providers are both confronted with actinic keratosis lesions very frequently. Because of the increasing age of the general population and the high recurrence rate of actinic keratosis, this condition

puts a high burden on the health care system, with 5 million dermatology visits per year in the United States alone.^{26,27} Our results could affect treatment choices in both dermatology and primary care. From a cost perspective, fluorouracil is also the most attractive option.²⁸ It is expected that a substantial cost reduction could be achieved with more uniformity in care and the choice for effective therapy.

This randomized trial has some limitations. Approximately half the patients who were assessed for eligibility declined to participate in this trial, usually because of personal preference or disfavor regarding a specific therapy. Patients' declining to participate is a common problem in randomized trials and may threaten external validity. The median age of the eligible trial population, 75 years, was similar to that of patients who participated, but the ratio of men to women was 4:1 in the eligible population and 9:1 in the trial population, which suggests that men were more willing to participate. Generalizability of the findings would be affected if the effectiveness of the evaluated treatments depends on sex, but sex-specific treatment response seems unlikely. To avoid substantial interobserver variation, all counts were performed by a single observer who was unaware of the treatment assignments. There may still be intraobserver variation, but random measurement errors result in nondifferential misclassification, which tends to dilute differences between baseline and follow-up counts of actinic keratosis lesions. However, potential underestimation of the reduction in actinic keratosis lesions will occur in all treatment groups and is unlikely to affect the comparison among groups.²⁹ Adherence to therapy with fluorouracil and imiquimod, which are applied for 4 consecutive weeks, was high in this trial (88.7% and 88.2%, respectively), but in daily practice, adherence may be lower. In this respect, ingenol mebutate, which is applied for only 3 consecutive days, had the advantage of better adherence (98.7%), but owing to the observed low probability of remaining free from treatment failure of only 28.9% in the long term, ingenol mebutate might be reserved for situations in which alternative treatments are not feasible.

In our trial, adherence was assessed by asking patients 2 weeks after the end of treatment how often they had used the therapy. This method may be subject to error.

Table 3. Adverse Events.*					
Event	Fluorouracil (N=135)	Imiquimod (N=121)	MAL-PDT (N=117)	Ingenol Mebutate (N=140)	P Value†
	<i>number (percent)</i>				
Any adverse event	125 (92.6)	103 (85.1)	113 (96.6)	134 (95.7)	0.004‡
During treatment					
Erythema	NA				
Moderate or severe	110 (81.5)	88 (72.7)		105 (75.0)	0.22
Absent or mild	25 (18.5)	33 (27.3)		35 (25.0)	
Swelling	NA				
Moderate or severe	41 (30.4)	53 (43.8)		59 (42.1)	0.050
Absent or mild	94 (69.6)	68 (56.2)		81 (57.9)	
Erosion	NA				
Moderate or severe	54 (40.0)	58 (47.9)		42 (30.0)	0.01
Absent or mild	81 (60.0)	63 (52.1)		98 (70.0)	
Crusts	NA				
Moderate or severe	77 (57.0)	83 (68.6)		53 (37.9)	<0.001‡
Absent or mild	58 (43.0)	38 (31.4)		87 (62.1)	
Vesicles or bullae	NA				
Moderate or severe	33 (24.4)	38 (31.4)		59 (42.1)	0.007‡
Absent or mild	102 (75.6)	83 (68.6)		81 (57.9)	
Scaling	NA				
Moderate or severe	60 (44.4)	51 (42.1)		50 (35.7)	0.31
Absent or mild	75 (55.6)	70 (57.9)		90 (64.3)	
Itching	NA				
Moderate or severe	84 (62.2)	74 (61.2)		58 (41.4)	0.001‡
Absent or mild	51 (37.8)	47 (38.8)		82 (58.6)	
Pain					
Severe	22 (16.3)	11 (9.1)	73 (62.4)	17 (12.1)	<0.001‡
Moderate	21 (15.6)	21 (17.4)	20 (17.1)	40 (28.6)	
Absent or mild	92 (68.1)	89 (73.6)	24 (20.5)	83 (59.3)	
Burning sensation					
Severe	29 (21.5)	12 (9.9)	78 (66.7)	30 (21.4)	<0.001‡
Moderate	34 (25.2)	30 (24.8)	22 (18.8)	42 (30.0)	
Absent or mild	72 (53.3)	79 (65.3)	17 (14.5)	68 (48.6)	
2 Wk after end of treatment					
Erythema	NA				
Moderate or severe	79 (58.5)	61 (50.4)	87 (74.4)	65 (46.4)	<0.001‡
Absent or mild	56 (41.5)	60 (49.6)	30 (25.6)	75 (53.6)	
Swelling	NA				
Moderate or severe	31 (23.0)	26 (21.5)	29 (24.8)	41 (29.3)	0.48
Absent or mild	104 (77.0)	95 (78.5)	88 (75.2)	99 (70.7)	

Table 3. (Continued.)

Event	Fluorouracil (N=135)	Imiquimod (N=121)	MAL-PDT (N=117)	Ingenol Mebutate (N=140)	P Value [†]
	<i>number (percent)</i>				
Erosion					
Moderate or severe	49 (36.3)	36 (29.8)	30 (25.6)	30 (21.4)	0.045
Absent or mild	86 (63.7)	85 (70.2)	87 (74.4)	110 (78.6)	
Crusts					
Moderate or severe	66 (48.9)	68 (56.2)	49 (41.9)	87 (62.1)	0.008‡
Absent or mild	69 (51.1)	53 (43.8)	68 (58.1)	53 (37.9)	
Vesicles or bullae					
Moderate or severe	28 (20.7)	17 (14.0)	22 (18.8)	35 (25.0)	0.17
Absent or mild	107 (79.3)	104 (86.0)	95 (81.2)	105 (75.0)	
Scaling					
Moderate or severe	77 (57.0)	46 (38.0)	70 (59.8)	93 (66.4)	<0.001‡
Absent or mild	58 (43.0)	75 (62.0)	47 (40.2)	47 (33.6)	
Itching					
Moderate or severe	75 (55.6)	47 (38.8)	56 (47.9)	85 (60.7)	0.003‡
Absent or mild	60 (44.4)	74 (61.2)	61 (52.1)	55 (39.3)	
Pain					
Severe	9 (6.7)	7 (5.8)	12 (10.3)	10 (7.1)	0.09
Moderate	15 (11.1)	9 (7.4)	21 (17.9)	24 (17.1)	
Absent or mild	111 (82.2)	105 (86.8)	84 (71.8)	106 (75.7)	
Burning sensation					
Severe	19 (14.1)	5 (4.1)	15 (12.8)	8 (5.7)	0.01
Moderate	18 (13.3)	14 (11.6)	17 (14.5)	32 (22.9)	
Absent or mild	98 (72.6)	102 (84.3)	85 (72.6)	100 (71.4)	

* Percentages may not total 100 because of rounding. NA denotes not applicable.

† All P values are for comparisons across all four treatment groups.

‡ A P value of 0.008 or less was considered to indicate statistical significance.

In conclusion, we found that after 12 months of follow-up, 5% fluorouracil cream was significantly more effective than 5% imiquimod cream, MAL-PDT, or 0.015% ingenol mebutate gel in the treatment of patients with multiple grade I to III actinic keratosis lesions on the head. No new toxic effects were identified in this trial.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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REFERENCES

1. Flohil SC, van der Leest RJ, Dowlatshahi EA, Hofman A, de Vries E, Nijsten T. Prevalence of actinic keratosis and its risk factors in the general population: the Rotterdam Study. *J Invest Dermatol* 2013;133:1971-8.
2. Spencer JM, Hazan C, Hsiung SH, Robins P. Therapeutic decision making in the therapy of actinic keratoses. *J Drugs Dermatol* 2005;4:296-301.
3. Siegel JA, Korgavkar K, Weinstock MA. Current perspective on actinic keratosis: a review. *Br J Dermatol* 2017;177:350-8.
4. Dinehart SM, Nelson-Adesokan P, Cockerell C, Russell S, Brown R. Metastatic cutaneous squamous cell carcinoma derived from actinic keratosis. *Cancer* 1997;79:920-3.
5. Ackerman AB, Mones JM. Solar (actinic) keratosis is squamous cell carcinoma. *Br J Dermatol* 2006;155:9-22.
6. Marks R, Rennie G, Selwood TS. Malignant transformation of solar keratoses to squamous cell carcinoma. *Lancet* 1988;1:795-7.
7. Lanoue J, Chen C, Goldenberg G. Actinic keratosis as a marker of field cancerization in excision specimens of cutaneous malignancies. *Cutis* 2016;97:415-20.
8. Glogau RG. The risk of progression to invasive disease. *J Am Acad Dermatol* 2000;42:23-4.
9. Criscione VD, Weinstock MA, Naylor ME, Luque C, Eide MJ, Bingham SF. Actinic keratoses: natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial. *Cancer* 2009;115:2523-30.
10. Frost C, Williams G, Green A. High incidence and regression rates of solar keratoses in a Queensland community. *J Invest Dermatol* 2000;115:273-7.
11. Pomerantz H, Hogan D, Eilers D, et al. Long-term efficacy of topical fluorouracil cream, 5%, for treating actinic keratosis: a randomized clinical trial. *JAMA Dermatol* 2015;151:952-60.
12. Weinstock MA, Thwin SS, Siegel JA, et al. Chemoprevention of basal and squamous cell carcinoma with a single course of fluorouracil, 5%, cream: a randomized clinical trial. *JAMA Dermatol* 2018;154:167-74.
13. Neugebauer R, Levandoski KA, Zhu Z, et al. A real-world, community-based cohort study comparing the effectiveness of topical fluorouracil versus topical imiquimod for the treatment of actinic keratosis. *J Am Acad Dermatol* 2018;78:710-6.
14. de Berker D, McGregor JM, Mohd Mustapa ME, Exton LS, Hughes BR. British Association of Dermatologists' guidelines for the care of patients with actinic keratosis 2017. *Br J Dermatol* 2017;176:20-43.
15. Beljaards RC, van der Sande A. Update richtlijn actinische keratosen 2017. *Nederlands Tijdschrift voor Dermatologie en Venereologie* 2017;27:190-2.
16. Werner RN, Stockfleth E, Connolly SM, et al. Evidence- and consensus-based (S3) guidelines for the treatment of actinic keratosis — International League of Dermatological Societies in cooperation with the European Dermatology Forum — short version. *J Eur Acad Dermatol Venereol* 2015;29:2069-79.
17. Gupta AK, Paquet M, Villanueva E, Brintnell W. Interventions for actinic keratoses. *Cochrane Database Syst Rev* 2012;12:CD004415.
18. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975;31:103-15.
19. Olsen EA, Abernethy ML, Kulp-Shorten C, et al. A double-blind, vehicle-controlled study evaluating masoprocol cream in the treatment of actinic keratoses on the head and neck. *J Am Acad Dermatol* 1991;24:738-43.
20. Leibold M, Dinehart S, Whiting D, et al. Imiquimod 5% cream for the treatment of actinic keratosis: results from two phase III, randomized, double-blind, parallel group, vehicle-controlled trials. *J Am Acad Dermatol* 2004;50:714-21.
21. Dirschka T, Gupta G, Micali G, et al. Real-world approach to actinic keratosis management: practical treatment algorithm for office-based dermatology. *J Dermatolog Treat* 2017;28:431-42.
22. Stockfleth E, Ferrandiz C, Grob JJ, Leigh I, Pehamberger H, Kerl H. Development of a treatment algorithm for actinic keratoses: a European Consensus. *Eur J Dermatol* 2008;18:651-9.
23. Stockfleth E, Kerl H. Guidelines for the management of actinic keratoses. *Eur J Dermatol* 2006;16:599-606.
24. Vegter S, Tolley K. A network meta-analysis of the relative efficacy of treatments for actinic keratosis of the face or scalp in Europe. *PLoS One* 2014;9(6):e96829.
25. Gupta AK, Paquet M. Network meta-analysis of the outcome 'participant complete clearance' in nonimmunosuppressed participants of eight interventions for actinic keratosis: a follow-up on a Cochrane review. *Br J Dermatol* 2013;169:250-9.
26. Kirby JS, Gregory T, Liu G, Leslie DL, Miller JJ. Variation in the cost of managing actinic keratosis. *JAMA Dermatol* 2017;153:264-9.
27. Gupta AK, Cooper EA, Feldman SR, Fleischer AB Jr. A survey of office visits for actinic keratosis as reported by NAMCS, 1990-1999: National Ambulatory Medical Care Survey. *Cutis* 2002;70:Suppl:8-13.
28. Medicijnkosten home page (<https://www.medicijnkosten.nl>).
29. Rothman KJ, Lash TL, Greenland S. *Modern epidemiology*. 3rd ed: Philadelphia: Lippincott Williams & Wilkins, 2012. Copyright © 2019 Massachusetts Medical Society.

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