

## Attitudes among dermatologists regarding actinic keratosis treatment options

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### Abstract

Actinic keratosis (AK) is considered a precancerous lesion that can develop into invasive squamous cell carcinoma. Its prevalence is increasing, and it is estimated that it affects between 1% and 44% of the adult population worldwide. Advanced age, fair skin phototypes, and cumulative sun exposure are the main risk factors for AK. Therapies for AK consists of lesion-directed treatment (*i.e.*, cryotherapy, curettage, electrocoagulation, and laser therapy) or field therapy [*i.e.*, photodynamic therapy (PDT), 5-fluorouracil (5-FU), diclofenac sodium (DIC), imiquimod (IMQ), and ingenol mebutate (Ing Meb)]. The type of therapy chosen is determined by the number and location of AKs, the patient's condition, and the patient's tolerability and compliance. In this survey, we collected information from 110 Italian dermatologists about their knowledge and attitudes toward various AK therapeutic approaches. In our study, we discovered that cryotherapy and PDT are the most used treatments for AK, while surgery and laser therapy are the least commonly used. The most commonly used topical therapies are DIC and IMQ 3.75 percent cream, followed by IMQ 5 percent cream, Ing Meb, and 5-FU. The correct treatment for AK can be difficult to choose, but adherence to therapy is critical for good results. Given the high and continuing rise in the incidence of AK, dermatologists' knowledge of various therapeutic approaches is critical.

### Introduction

Actinic keratosis (AK) is mostly considered as a precancerous lesion that may evolve into an invasive squamous cell carcinoma (SCC)<sup>1</sup> However, AK has been

defined as a carcinoma in situ and still now there are some controversies regarding its real definition. The prevalence of AK has been estimated worldwide to be between 1% and 44% of the adult population.<sup>2</sup> The main risk factors for developing AK are advanced age, fair skin phototypes and cumulative sun exposure.<sup>3</sup> In addition, the prevalence of AK is higher in men than women due to greater UV exposure in men, mainly on the scalp. In the European population aged >70 years, the prevalence of AK has been estimated to be 34% in men and 18% in women.<sup>4</sup> Currently the incidence of AK is increasing due to the higher life expectancy and to the inappropriate sun exposure behaviors.

The clinical features of AK are variable. More frequently it is a pink macule or plaque with fine desquamation, flat or hyperkeratotic. Sometimes AK is pigmented, especially when it appears on the face or on the scalp. Considering Olsen's classification, there are three grades of AK based on the intraepithelial location of atypical keratinocytes.<sup>4</sup> AK I and II are superficial lesions that could spontaneously regress, while AK III, is a hyperkeratotic lesion with atypical keratinocytes involving the entire epidermis and may evolve to invasive SCC.

AKs could be multiple and usually appear on areas chronically exposed to UV radiation defined as field of cancerization. In this area, the skin surrounding the AKs is characterized by subclinical changes displaying the same genetic changes found in the lesion itself.<sup>5</sup> The diagnosis of AK is mainly clinical and/or dermoscopic but, in specific cases, reflectance confocal microscopy can be utilized to distinguish it from other benign or malignant tumors. In uncertain cases, when the progression into invasive SCC is suspected, a skin biopsy with histological examination is recommended.

Two therapeutic approaches are available to treat AK: lesion-directed treatment to target single lesions or field therapy to treat multiple AKs and the surrounding areas of photodamaged skin.<sup>1,6</sup> In case of single lesions ( $\geq 1$  and  $\leq 5$  lesions), ablative therapy is preferred and includes cryotherapy, curettage, electrocoagulation, and laser therapy. Other treatments such as piroxicam could be utilized for AK single lesions.<sup>7</sup>

A field therapy, consisting of topical treatments with or without photodynamic therapy (PDT), is recommended to treat multiple AKs ( $\geq 6$  lesions) and the underlying area of photodamage. According to current international recommendations, field treatments include 5-Fluorouracil (5-FU) available at different percentage (0.5% 5-FU, 0.5% 5-FU in association with 10%

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Availability of data and material: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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salicylic acid, 1% 5-FU, 2% 5-FU, 5% 5-FU), diclofenac sodium (DIC; 3%), imiquimod (IMQ; 2.5%, 3.75%, 5%), ingenol mebutate (Ing Meb; 0.015%, 0.05%), 5-aminolevulinic acid (ALA) plus PDT and methyl aminolevulinate (MAL; 16.0%, 16.8%) plus PDT. The choice of therapy depends on the number and localization of AKs, patient's condition, and the patient's tolerability and compliance.<sup>1,8</sup>

The aim of this study was to evaluate

the knowledge and attitude among dermatologists towards different therapeutic approaches specific for AK.

## Materials and methods

The present data were extracted from a survey conducted on a sample of dermatologists recruited by other dermatologists according to a snowball sampling procedure. The study was approved by Institutional Ethical Committee of IDI-IRCCS in Rome (Approval # 608-1) and was conducted in accordance with the Declaration of Helsinki. A questionnaire was sent by email to all clinicians, describing the purpose of the study. Dermatologists who agreed to participate signed a written informed consent before starting the study. Data were collected from June 16<sup>th</sup>, 2020, to August 1<sup>st</sup>, 2020. The questionnaire consisted of two parts.

The first part included personal data from participant: gender, age, number of years since they finished dermatology residency (<10, 10-19, ≥20), geographical area (Northern, Central, or Southern Italy), workplace (hospital, university/research hospital, local health department, private

practice) (Table 1).

The second part consisted in specific questions regarding knowledge and attitude towards different therapeutic approaches for AK (Table 2).

Data were described as numbers, percentages, and frequency rates. Results were compared in different subgroups of participants, according to gender, years since finishing dermatology training, geographical area, and workplace, using the chi-square test. Data were analyzed using IBM SPSS Statistics for Windows, Release 26.0.0.1 (IBM Corp., Armonk, NY, USA).

## Results

The study participants were one hundred and ten dermatologists. There were 57 women (51.8%) and 53 (48.2%) men. More than 30% of them had finished dermatology training since less than 10 years, 25.5% since 10 to 19 years, and 43.6% in the last 20 years or more. The description of the study population and trends in therapeutic choices are shown in Tables 1 and 2.

Concerning therapeutic approaches, the most frequent are cryotherapy and PDT. Some dermatologists (26.4%) prescribed

cryotherapy for 75% of AK cases whereas others (29.1%) for 50% of AK cases. As for PDT, 20.9% of participants prescribed it for 50% of AK cases, while 17.3% never used it. Surgery and laser therapy are the less frequent utilized therapeutic options. Notably, 53.7% of participants never prescribed surgery. Similarly, 46.4% of dermatologists never prescribed laser therapy for AK. However, laser therapy is utilized for 5% of AKs by 24.5% of participants and surgery by 28.2%.

As for topical therapy, the results are variable. The most frequent topical therapies utilized in 50% of AKs are IMQ 3.75% cream prescribed by 9.1% of participants and DIC used by 14.5% of them. Despite this, 41.8% of dermatologists never prescribed IMQ 3.75% and 20.0% of them never used DIC. Moreover, IMQ 5% cream is prescribed by 5.5% of participants for 50% of AKs and by 23.6% of them for 25% of AKs. Among dermatologists who participated in the survey, 80.9% never used Ing Meb and 52.7% never prescribed piroxicam. Few dermatologists (6.4%) prescribe Ing Meb for 5% of AKs while 23.6% of them prescribed piroxicam. As regards 5-FU, 7.3% of dermatologists prescribed it for 50% of AKs and 40.9% of them never used

**Table 1. Description of the sample and relationship between sociodemographic features and therapeutic choices for AK (N=110).**

Dermatologists			Percentage of used treatments for AK				
			Diclofenac <sup>1</sup>	Imiquimod 3.75% <sup>2</sup>	Ingenolo <sup>3</sup>	Piroxicam <sup>4</sup>	Laser
Column %			80.0	58.2	19.1	47.3	53.6
Sex	Female	51.8	82.5	52.6	21.1	54.4	56.1
	Male	48.2	77.4	64.2	17.0	36.6	50.9
Years since specialization	<10	30.9	82.4	67.6	20.6	50.0	61.8
	10-19	25.5	86.2	65.5	24.1	69.0	62.1
	20-29	10.9	63.6	54.5	9.1	27.3	36.4
	≥30	32.7	77.8	44.4	16.7	3.3	44.4
Area	Northern	22.7	88.0	76.0	8.0	41.9	72.0
	Central	56.4	72.6	56.5	19.4	68.0	48.4
	Southern	20.9	91.3	43.5	30.4	39.1	47.8

<sup>1</sup>Diclofenac x Area =  $\chi^2$  M-H Treand: 0.023 p<0.05. <sup>2</sup>Imiquimod 3.75% x yrs of specialization:  $\chi^2$  M-H Treand = 0.42 p<0.05. <sup>3</sup>Ingenolo x Area:  $\chi^2$  M-H Treand =0.03, p<0.05. <sup>4</sup>Piroxicam x yrs of specialization ("<10 to 19" group vs the other groups "20 - >30"):  $\chi^2$ mid-P=0.006 p<0.05.

**Table 2. Description of the answers of dermatologists to the question concerning AK therapy approaches (N=110).**

Therapeutic approaches	In percentage, for every 100 new AK, I prescribed...							
	Never	5%	10%	25%	50%	75%	Always	Missed, %
Surgery	53.7	28.2	12.7	3.6	0.9	-	-	0.9
Cryotherapy	10	10	7.3	10	29.1	26.4	7.3	-
Photodynamic therapy	17.3	13.6	20.9	17.3	20.9	10.0	-	-
Imiquimod 5%	36.4	18.2	15.5	23.6	5.5	0.9	-	-
Imiquimod 3.75%	41.8	11.8	14.5	18.2	9.1	4.5	-	-
Diclofenac	20.0	11.8	15.5	28.2	14.5	10.0	-	-
5-fluorouracile	40.9	19.1	17.3	13.6	7.3	1.8	-	-
Ingenolo	80.9	6.4	6.4	5.5	0.9	-	-	-
Piroxicam	52.7	23.6	13.6	7.3	2.7	-	-	-
Curattage-laser	46.4	24.5	15.5	8.2	4.5	0.9	-	-

it. Furthermore, laser therapy is more utilized in Northern (72%) compared to Central (48.4%) and Southern Italy (47.8%) while Ing Meb is more used in Southern (30.4%) compared to Northern (8.0%) and Central (19.4%) Italy (Table 1).

Considering the years since specialization, dermatologists who had finished Dermatology training since less than 10 years prescribed IMQ 3.75% more than older colleagues (>10 ys. = 67.6%, 10-19 ys. = 65.5%, 20-29 ys. = 54.5%, ≥30 ys. = 44.4%). Moreover, piroxicam is mainly prescribed by younger dermatologists (>10 ys. = 50%, 10-19 ys. = 69.0%) compared to older colleagues (20-29 ys. = 27.3%, ≥30 ys. = 3.3%).

## Discussion

In our survey, cryotherapy is the most used treatment by dermatologists for AK. Cryotherapy is recommended by guidelines to treat single AK lesion,<sup>1,9</sup> but sometimes it can be used also to treat multiple AKs, mainly in the elderly with photodamaged skin. PDT, which is preferable as field therapy to treat multiple AKs, is prescribed by 20.9% dermatologists for 50% of AKs and by 10% of them for 75% of AKs. However, in our sample, 17.3% of participants did not prescribe PDT probably because not all medical institutions have facilities to disperse this therapy or because some dermatologists are not confident to use traditional PDT or day light PDT. Another reason could be that PDT is an expensive treatment and, dependently from National Health System, there could be few hospitals that offer it without any payments.<sup>10</sup>

Surgery, instead, is the less common therapeutic option: 53.7% of dermatologists never prescribed it and 28.2% used it only for 5% of AK cases. In fact, surgery is not recommended by guidelines to treat AK but it is needed in uncertain cases that could progress to an invasive SCC.<sup>11,12</sup>

Regarding laser therapy, about 50% of dermatologists never require it and about 35% prescribed it in 5-15% of AKs. A reason to explain this result is that laser therapy is more expensive compared to cryotherapy. Besides, CO<sub>2</sub> laser ablation is not superior to cryotherapy for the treatment of isolated AKs of the face and of the scalp, as reported in a randomized clinical trial.<sup>13</sup>

As regards to topical therapeutic options, the results are variable. DIC was the most prescribed topical product for AK. About 80% of interviewed dermatologists used it for AK and in particular about 25% prescribed it for 50-75% of AK cases. These results can be explained due to the efficacy

and safety of DIC, which is mainly active only for AK type I. It could be quite well tolerated also by elderly patients because side effects, such as mild erythema or itching, generally are rarer compared to IMQ.<sup>14</sup>

IMQ is present in two different percentage (5% and 3.75%) in Italy. Our survey showed that 3.75% IMQ is more prescribed than 5% IMQ. Specifically, for 50-75% of AKs, 3.75% IMQ is prescribed by about 15% of dermatologists while 5% IMQ is used by about 6% of them. Both topical immunotherapy with IMQ (*i.e.*, 3.75% and 5%) are effective to treat the whole cancerization field but they cannot be used in patients who have received an organ transplant. According to international guidelines regarding AK therapies, IMQ 5% has to be applied 3 days a week for 6 weeks while IMQ 3.75% is used for 14 consecutive days a month for 2 months. The different posology and the lower side effects for IMQ 3.75% could explain the major used of this percentage of IMQ as showed in our data.

Regarding 5-FU, a recent systematic review and network meta-analysis reported that this topical therapy has the best efficacy and safety profile compared with other field-directed therapies for AKs. This analysis included 5 randomized clinical trials which assessed 4% 5-FU, 5% 5-FU and 0.5% 5-FU in 10% salicylic acid solution.<sup>15</sup> 4% 5-FU cream with once daily application has been approved for the treatment of non-hyperkeratotic, non-hypertrophic AK and it was more tolerated than 5% 5-FU.<sup>16</sup> Despite this, in our sample only 60% of interviewed dermatologists prescribed 5-FU, and only 9% of them utilized 5-FU for 50-75% of AKs. 40% of participants have never used 5FU. These limited used of this topical therapy could be due to the recent introduction of 5-FU in Italy for the treatment of AK. In Italy the only formulation available for the treatment of AK, when the survey has been performed in 2020, was 0.5% 5-FU in association with 10% salicylic acid. A new product 4% 5 FU cream has been approved also in Italy since September 2021.

Moreover, in our sample about 80% of participants declared not to use Ing Meb. This topical therapy has been approved by FDA for multiple non hypertrophic and non-hyperkeratotic AKs on a field of cancerization in January 2012.<sup>17</sup> Despite it could provoke moderate-severe side effects after the treatment, it was acceptable for patients for its efficacious and because it had to be used for only 3 days on the scalp and for 2 days on the trunk.<sup>18,19</sup> However, in 2020 the market authorization for Ing Meb in the European Union was withdrawn because this drug was proven to be associated to an increase of skin cancer.<sup>20</sup>

As regards piroxicam, about 50% of dermatologists declared not to prescribe it and about 35% used it for 5-10% of AKs. These data can be understandable considering that this product is utilized for the treatment of AK or to prevent the development of new AK on photodamaged area, but it is not recommended by European and Italian Guidelines.<sup>1,21</sup> Furthermore, the multivariable model showed that dermatologists who had finished their training more recently were more used to prescribe piroxicam than the older ones.

It is interesting to observe that laser therapy is more utilized for AKs in Northern compared to Central Italy probably due for the major availability in the first region. Otherwise, DIC is more used in Southern Italy while IMQ is prescribed more in Northern Italy. This difference could be due to the fact that dermatologists from Southern Italy prefer to use DIC because it gives less side effects than IMQ.

The result of our study seems in line with a recent Italian consensus<sup>21</sup> and with European guidelines.<sup>1,22</sup> Cryotherapy is the most used treatment for patients with few AK (less than 5 scattered AKs or less than 3 AKs in an area of 25 cm<sup>2</sup>), while PDT and IMQ cream are preferred for patients with multiple AKs (5 or more AKs or 3 or more AKs in an area of 25 cm<sup>2</sup>).<sup>21</sup>

Considering that AK could be a chronic disease, most dermatologists are used to have a combination approach with multiple treatment for AK.<sup>23</sup> Specifically, a field therapy with IMQ 3.75% can be prescribed after cryotherapy to obtain a better clearance of AK, and similarly cryotherapy can follow PDT or other topical treatment.

The results of our survey confirm that the real-world therapeutic approach is variable, and the goal of treatment is AK reduction and long-term disease control to prevent SCC development. The challenge for every dermatologist is to choose the proper treatment for every patient, considering not only the clinical presentation and number of AK, but also patient's condition such as age, comorbidity, immunosuppression, and adherence to treatment.<sup>22</sup>

A limitation of our study is the restricted number of the considered dermatologists and the fact that the questionnaire did not distinguish the treatment for singles AKs or for multiple AKs in a field of cancerization.

## Conclusions

We found that the most frequently used treatments for AKs by Italian dermatologists are cryotherapy, PDT and topical agents, such as DIC and IMQ. Our results

highlight that choice the appropriate treatment for AK can be challenging and should be adopted to every patient because adherence to therapy plays a key role to obtain good results. Besides, AK should be considered a chronic disease in patients with severe photodamage, and different therapies could be used consecutively to obtain a complete skin clearance and to prevent the development of SCC.

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