BJD
British Journal of Dermatology

Cryotherapy is preferable to ablative CO_2 laser for the treatment of isolated actinic keratoses of the face and scalp: a randomized clinical trial*

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Accepted for publication
20 January 2014

Funding sources
No external funding.

Conflicts of interest
None declared.

*Plain language summary available online

DOI 10.1111/bjd.12847

Summary

Background Actinic keratosis (AK) may progress to squamous cell carcinoma. In the case of normal or mildly photodamaged skin, lesion-directed treatments are considered valuable options despite poor published evidence of their therapeutic activity.

Objectives The aim of this single-centre, open-label, prospective, nonsponsored, randomized, controlled clinical trial was to compare CO_2 laser ablation with cryotherapy in the treatment of isolated AKs of the face and scalp.

Patients and methods Patients with isolated (≤ 4) AKs of the face and scalp were randomized to receive CO_2 laser ablation or cryotherapy. After 90 days, the overall complete remission (CR) rates of patients and lesions were assessed and correlated with thickness grade.

Results Two hundred patients with a total number of 543 AKs were enrolled. The CR rates of lesions after 3 months were 78·2% with cryotherapy and 72·4% with CO_2 laser ablation. Thicker lesions were significantly more responsive to cryotherapy ($P = 0{\cdot}034$). Seventy-three patients (71·6%) had CR of all lesions 3 months after cryotherapy and 64 (65·3%) after laser ablation. At 12 months after treatment the number of patients with CR was reduced to 53 with cryotherapy and 14 with laser ablation.

Conclusions The rate of patients and lesions with CR is similar after 3 months, but more patients remain in stable remission for 12 months after cryotherapy. Cryotherapy is more effective for thick lesions. The cosmetic outcome was good or excellent in almost all patients.

What's already known about this topic?

- Actinic keratosis (AK) has the potential to progress to squamous cell carcinoma.
- If single or few AKs develop on normal or mildly photodamaged skin, lesion-directed treatments are considered valuable options despite poor knowledge of their therapeutic activity.

What does this study add?

- The rate of patients with complete remission and lesions with complete remission is similar after 3 months after both cryotherapy and CO_2 laser treatment, but with cryotherapy more patients remain in stable remission after 12 months.
- Cryotherapy is also more effective for thick lesions.

The prevalence of actinic keratosis (AK) is high and steadily increasing worldwide among white-skinned people.[1,2] There is general consensus that AK lesions should be removed because of their potential to progress to invasive squamous cell carcinoma.[3–6]

Because of its prevalence, AK is among the most commonly treated skin conditions in the outpatient setting.[7] The healthcare cost of managing AKs is high and growing. Several effective treatment options are available. Each of these has its own profile of efficacy, tolerability, safety, ease of use and cost effectiveness. The therapeutic strategy depends primarily on the number of lesions and the overall appearance of the surrounding skin. If lesions are isolated and fewer than five, and the surrounding skin shows no or mild clinical manifestations of photodamage, lesion-targeted treatment modalities, namely cryotherapy and ablative CO_2 laser, are considered the most valuable treatment options.[4,5,8–10]

Despite their common application, the efficacy and safety of these therapies in the treatment of this subgroup of patients remain to be clarified.[6,11] Indeed, their efficiency has been investigated in the treatment of patients with multiple AKs on photodamaged skin in a setting of field cancerization.[12,13] In this clinical situation, cryotherapy and CO_2 laser therapy were found to be equally or less effective in comparison with field-directed treatments, such as photodynamic therapy,[12,14–17] imiquimod and 5-fluorouracil.[18] In addition, cosmetic outcome and patient evaluation were less favourable for lesion-directed treatments.

The aim of this single-centre, open-label, prospective, nonsponsored, randomized, controlled clinical trial was to compare cryotherapy with CO_2 laser ablation for the treatment of isolated AKs of the face and scalp in patients with no or mild clinical signs of photoageing. In addition, cost-effectiveness was analysed as a contribution to the Health Technology Assessment.

Patients and methods

Patients

Adult white-skinned patients (skin types I–IV) with a maximum of four AKs of the face and/or scalp and no or mild clinical manifestations of photoageing of the surrounding skin were enrolled.[19] They were seen from May 2011 to October 2012 at the outpatient clinic of the Department of Dermatology of the University of Brescia, a tertiary referral centre for skin cancer in Northern Italy. Exclusion criteria were pregnancy or lactation; active severe systemic infectious disease; moderate or severe photodamage,[19] or other inflammatory or neoplastic diseases of the surrounding skin; allergy to local anaesthetics; and likelihood of poor compliance. All patients were instructed to avoid intentional sun exposure, to wear hats and protective clothing, and to daily apply a potent sunscreen (sun protection factor > 50) as protection from unintentional sun exposure. The diagnosis was assessed visually only in most cases. Dermoscopy or skin biopsies were done only if the diagnosis was clinically not unequivocal. The overall thickness of each lesion was classified into grades I–III according to Olsen *et al.*:[20] grade I, mild (slightly palpable AK, more easily felt than seen); II, moderate (moderately thick AK, easily felt); and III, severe (very thick or obvious AK).[20] The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the local ethics committee. Patients signed an informed consent form before enrolment. The study was funded by the University of Brescia as part of a programme of Health Technology Assessment.

Treatment procedure

At baseline, patients were enrolled and randomized to receive cryotherapy or laser ablation, and photodocumentation of lesions was undertaken. Randomization with a 1 : 1 allocation ratio was done by telephone with a computer-generated list using random permuted blocks of six to ensure concealment of allocation. Patients and treating physicians were not blinded to group assignment. Follow-up, data collection of clinical outcome and assessment of cosmetic outcome was done by one physician (P.C.P.), who was blinded to treatment assignment.

For cryotherapy, a cotton tip soaked with liquid nitrogen was applied on the lesion surface for 10–20 s until a 1–2-mm perilesional frozen rim was achieved.[21]

A single session of CO_2 laser (Spectra-SP™, Lutronic Corporation, Cyeonggi, Korea) ablation was delivered. Two to three laser passes resulted in epidermal ablation, as evidenced by punctate dermal bleeding. The laser was applied in char-free mode, using 500-μs pulses at a power of 2·3 W with a 50-Hz repetition rate. CO_2 laser treatment was done under local anaesthesia with lidocaine 2% (Astrazeneca, Milan, Italy).

Following either treatment gentamicin 0·1% cream (Schering Plough, Milan, Italy) was applied twice daily until the defect was completely re-epithelized.

Response evaluation

Response rates at 3 and 12 months after cryotherapy or CO_2 laser ablation were compared both on a per-patient and on a per-lesion basis.

In the per-patient analysis, the response after 3 months was categorized as 'complete' (CR), 'partial' (PR) and 'no response' (NR). For complete responders only a follow-up evaluation was performed at 12 months after intervention.

In the per-lesion analysis, the response after 3 and 12 months (only in patients with CR after 3 months) was dichotomized as CR (complete disappearance of the lesion at both visual assessment and palpation) or noncomplete (NR) (no or incomplete disappearance of the lesion). The response rates of lesions as a function of the thickness grade were also investigated.

If lesions were resistant to treatment after 3 months or recurrences were seen after 12 months, they were always treated with cryotherapy.

Using a standard 1–10 visual analogue scale (VAS) pain was scored by patients who underwent cryotherapy.

Short-term adverse events were recorded on the same day after the treatment and after 2 weeks by telephone interview. Long-term adverse effects were registered at follow-up examinations. In addition, patients were instructed to contact the treating centre, without hesitation, if they developed any local and systemic adverse event that could be related to the treatment.

The overall cosmetic outcome of patients with CR of all lesions was assessed by both a blinded investigator (P.C.P.) and the patients themselves 3 months after the treatment. It was graded into excellent (no or mild redness or change in pigmentation), good (moderate redness or change in pigmentation), fair (slight-to-moderate scarring, atrophy or induration) and poor (extensive scarring, atrophy or induration).[22] After 3 months, all subjects anonymously rated their overall satisfaction with the treatment as excellent (very satisfied), good (moderately satisfied) or fair (slightly or not satisfied).

Pharmacoeconomic evaluation

We calculated the cost of the two treatment procedures (assuming that the total standard time of the procedure is 20 min for both treatments) by adding the costs of healthcare providers on the basis of hourly standard cost for hospital personnel in Italy (70 Euros for the physician and 30 Euros for the nurse)[23] and supplies costs (disposable materials, local anaesthetic, liquid nitrogen, amortization/depreciation of instruments, electrical supply and gentamicin cream for post-treatment wound management), plus overhead costs (20% of total). The cost-effectiveness ratio was calculated by dividing the total cost of the treatment of all patients by the number of patients with CR of all lesions.

Statistical methods

In the per-patient analysis of efficacy, the proportions of responders and relapsed patients were compared between treatments using a χ^2 test, which was also used for comparisons of overall cosmetic outcome and overall patient satisfaction.

For the per-lesion analysis, to take into account the clustering effect within patients, generalized estimating equations logistic models were used to assess the treatment effect.[24] The agreement of cosmetic outcome evaluation between investigator and patient was assessed by Cohen's kappa coefficient.

Analyses were performed using STATA 11 (Stata Statistical Software, Release 11, 2009; StataCorp LP, College Station, TX, U.S.A.).

No statistical sample size calculation had been performed when the study was designed. Our decision to enrol 100 patients per group was based on the sample size reported in a similar trial.[14] With this sample size we had a power of 80% to detect an absolute difference in the CR proportions between the two groups > 15% ($\alpha = 0{\cdot}05$, χ^2 test).

Results

Efficacy

Two hundred patients (128 men, 72 women) with one to four AKs of the face and scalp with no or mild clinical features of photoageing[19] were enrolled and completed the study. Patients with NR or PR after 90 days exited the study at that time; patients with a CR were followed for a total of 12 months.

Ninety-eight patients were randomized to treatment with CO_2 laser ablation and 102 to cryotherapy. The treatment groups were comparable with respect to age, sex and number of lesions per patient (Table 1).

Unexpectedly, the distribution of lesions according to their thickness was significantly different between groups ($P < 0{\cdot}0001$). We observed a higher rate of grade I lesions in the laser treatment group and a higher rate of grade II lesions in patients treated with cryotherapy (Table 1). In order to account for this observed disparity between treatment, groups, the per-lesion analyses comparing the overall treatment effects were adjusted for lesion grade.

The flowchart of the study and number of responders are summarized in Figure 1.

The rate of patients with CR of all lesions was 71·6% (73 of 102 patients) 3 months after cryotherapy and 65·3% (64 of 98 patients) after laser ablation. This difference was not statistically significant ($P = 0{\cdot}532$) (Table 2).

The per-lesion analysis showed that, after 3 months, the overall CR rates with cryotherapy and laser ablation were

Table 1 Patients demographics and disease characteristics at baseline[a]

	Cryotherapy (n = 102)	CO_2 laser ablation (n = 98)
Age (years), mean ± SD (min–max)	71 ± 9 (52–90)	71 ± 12 (39–98)
Sex		
Female	38 (37·3%)	34 (34·7%)
Male	64 (62·7%)	64 (65·3%)
No. of lesions per patient		
1	20 (19·6%)	31 (31·6%)
2	22 (21·6%)	13 (13·3%)
3	15 (14·7%)	19 (19·4%)
4	45 (44·1%)	35 (35·7%)
Total no. of lesions	289 (100%)	254 (100%)
Lesion grade[b]		
Grade I (thin)	9 (3·1%)	33 (13·0%)
Grade II (moderate)	184 (63·7%)	134 (52·8%)
Grade III (thick)	96 (33·2%)	87 (34·3%)

[a]Because of rounding, not all percentages total 100; [b]$P < 0{\cdot}0001$ (based on a χ^2 test comparing the distribution of the lesion grade between treatments); in order to take into account this observed and unexpected imbalance between treatments, the per-lesion analyses comparing the treatment overall effects were adjusted by lesion grade.

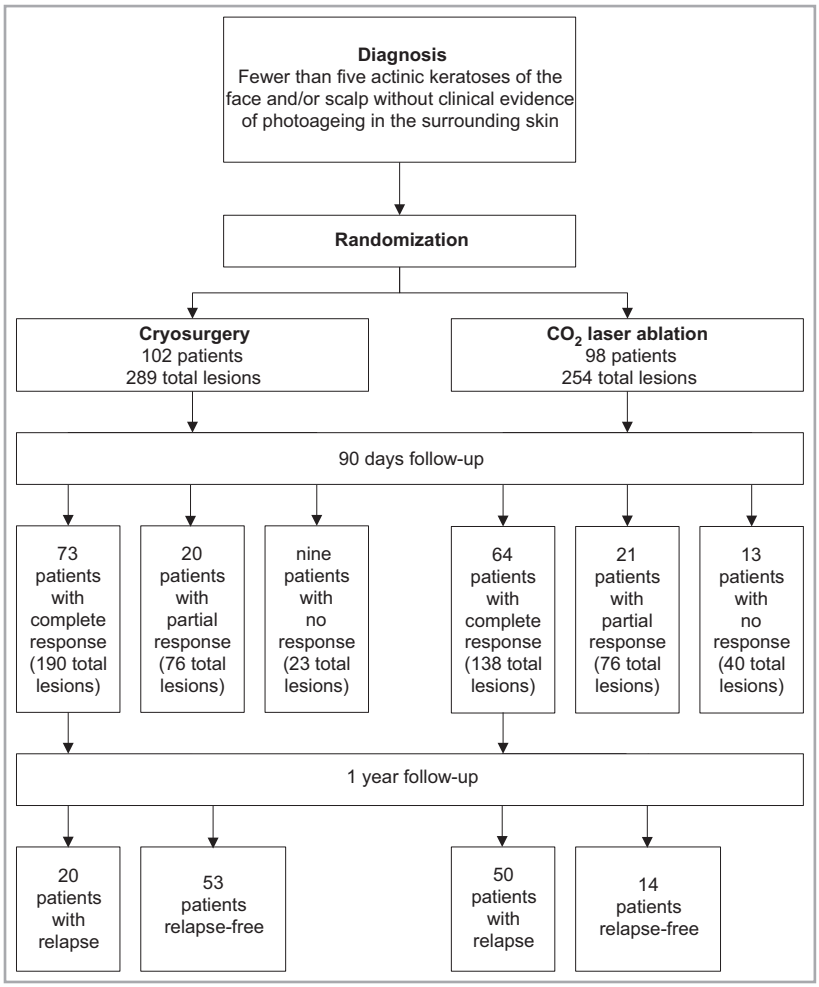

Fig 1. Flowchart of the study and therapeutic responses.

Table 2 Response at 90 days and at 1 year; per-patient analysis[a]

	Cryotherapy	CO_2 laser ablation	P-value[b]
At 90 days (all patients)	102 patients	98 patients	
Response			
No response	9 (8·8%)	13 (13·3%)	0·532
Partial	20 (19·6%)	21 (21·4%)	
Complete	73 (71·6%)	64 (65·3%)	
At 1 year (only complete responders at 90 days)	73 patients	64 patients	
Relapse			
Yes	20 (27·4%)	50 (78·1%)	< 0·0001
No	53 (72·6%)	14 (21·9%)	

[a]Because of rounding, not all percentages total 100; [b]χ^2 test.

similar and equal to 78·2% (226 of 289 treated lesions) and 72·4% (184 of 254), respectively. Unlike grade I and grade II lesions, thick grade III lesions were significantly (P = 0·034) more responsive to cryotherapy (77 of 96; 80·2%) than to CO_2 laser ablation (52 of 87; 59·8%) (Table 3).

Patients with CR of all lesions were followed beyond 3 months. After 12 months, the number of patients without relapse was significantly different (P < 0·0001): 53 of 73 (72·6%) with cryotherapy and 14 of 64 (21·9%) with CO_2 laser ablation (Table 2). In these patients, the overall final response rate of lesions was 66·8% (127 of 190 lesions) with cryotherapy and 37·0% (51 of 138 lesions) with CO_2 laser ablation (P = 0·0016). With respect to the lesion thickness, grade II lesions were significantly more responsive (P < 0·0001) to cryotherapy (96 of 121; 79·3%) than to CO_2 laser ablation (31 of 83; 37·3%) (Table 3).

Cosmetic outcome

After 3 months, the cosmetic outcomes of patients with CR were similar between treatments (P = 0·401), with an excellent or good result in the vast majority of patients and a substantial agreement between a blinded investigator (P.C.P.) and the patients themselves (Table 4). The blinded investigator rated as excellent, good and fair the cosmetic outcome of 37 (50·7%), 26 (35·6%) and 10 (13·7%), respectively, patients treated with cryotherapy, and 31 (48·4%), 28 (43·8%) and 5 (7·8%), respectively, patients treated with laser ablation. The

Table 3 Response at 90 days and at 1 year; per-lesion analysis

	Cryotherapy	CO_2 laser ablation	P-value[a]
At 90 days (all patients)	289 lesions evaluated (102 patients)	254 lesions evaluated (98 patients)	
Lesion grade			
I (thin)	8/9 (88·9%)	24/33 (72·7%)	0·274
II (moderate)	141/184 (76·6%)	108/134 (80·6%)	0·543
III (thick)	77/96 (80·2%)	52/87 (59·8%)	0·034
Overall response	226/289 (78·2%)	184/254 (72·4%)	0·258[b]
At 1 year (only complete responders at 90 days)	190 lesions evaluated (73 patients)	138 lesions evaluated (64 patients)	
Lesion grade			
Grade I (thin)	2/5 (40·0%)	8/21 (38·1%)	0·956
Grade II (moderate)	96/121 (79·3%)	31/83 (37·3%)	< 0·0001
Grade III (thick)	29/64 (45·3%)	12/34 (35·3%)	0·584
Overall response	127/190 (66·8%)	51/138 (37·0%)	0·0016[b]

[a]Based on the results of generalized estimating equations logistic models; [b]adjusted by lesion grade.

Table 4 Overall cosmetic outcome (only in patients with complete remission at 90 days)[a]

	Cryotherapy (73 patients)	CO_2 laser ablation (64 patients)	P-value[b]
Investigator assessment			
Poor	0 (0·0%)	0 (0·0%)	0·430
Fair	10 (13·7%)	5 (7·8%)	
Good	26 (35·6%)	28 (43·8%)	
Excellent	37 (50·7%)	31 (48·4%)	
Patient assessment			
Poor	0 (0·0%)	0 (0·0%)	0·401
Fair	5 (6·8%)	3 (4·7%)	
Good	25 (34·2%)	29 (45·3%)	
Excellent	43 (58·9%)	32 (50·0%)	

[a]Because of rounding, not all percentages total 100; [b]chi-square test.

patients rated their own cosmetic outcomes as excellent, good and fair in 43 (58·9%), 25 (34·2%) and 5 (6·8%), respectively, treatment with cryotherapy, and 32 (50%), 29 (45·3%) and 3 (4·7%), respectively, treatments with laser ablation. A poor cosmetic outcome with extensive scarring, atrophy or induration was never registered.

The agreement in the assessment of the overall cosmetic outcome between investigators and patients was good both in the cryotherapy (Cohen's kappa: 0·64) and in the laser groups (Cohen's kappa: 0·72). In the cryotherapy group, 13 patients assessed their cosmetic outcomes more favourably than the investigator, while the opposite was true in two cases. In the CO_2 laser ablation group, six patients gave an assessment of the cosmetic outcome better than the assessment by the investigator, while the opposite was true in four cases.

Safety, tolerability and patient satisfaction

Soon after cryotherapy, variable degrees of erythema and oedema were seen, and serous and haemorrhagic vesicles and blisters developed in the following few hours and left erosions and crusts. Erosions and crusts also developed after CO_2 laser. The VAS score (mean ± SD) of cryotherapy was moderate: 5·2 ± 2·4. Local or systemic long-term adverse events that could be related to treatment were not reported by patients nor found at the follow-up visits.

Sixty-one (59·8%) and 41 (40·2%) patients treated with cryotherapy scored their overall satisfaction as excellent and good, respectively, whereas 24 (24·5%), 56 (57·1%) and 18 (18·4%) of patients with laser ablation scored it as excellent, good or fair, respectively. The difference in favour of cryotherapy was statistically significant ($P < 0·0001$) (Table 5).

Pharmacoeconomic evaluation

In the setting of the Italian National Health System, the cost of cryotherapy is 44.80 Euros and the cost of CO_2 laser ablation is 46.00 Euros (Table 6).

The cost-effectiveness analysis shows that the costs per patient with CR after 3 months were 57.40 Euros with cryotherapy and 70.80 Euros with laser ablation, and the costs per

Table 5 Overall patient satisfaction[a]

	Cryotherapy (102 patients)	CO_2 laser ablation (98 patients)	P-value[b]
Fair	0 (0%)	18 (18·4%)	< 0·0001
Good	41 (40·2%)	56 (57·1%)	
Excellent	61 (59·8%)	24 (24·5%)	

[a]Because of rounding, not all percentages total 100; [b]χ^2 test.

Table 6 Costs (Euros) of the treatment procedures for the Italian National Health System

	Cryotherapy	CO_2 laser ablation
Doctor	23·34	23·34
Nurse	10·00	10·00
Disposable materials	2·00	2·00
Other office costs (local anaesthetic, liquid nitrogen, electrical supply, depreciation of instruments)	2·00	3·00
Overhead costs (20%)	7·46	7·66
Total	44·80	46·00

patient with CR after 12 months were 86.20 Euros and 328.60 Euros, respectively.

Discussion

To our knowledge, this is the first randomized clinical investigation of the treatment results of CO_2 laser ablation and cryotherapy in patients affected by isolated AKs of the face and scalp. Both treatments were well tolerated, safe, effective and cheap, but we found an overall superiority of cryotherapy.

Indeed, with both treatments, the rate of patients with CR of all lesions and the overall cure rates of lesions were high after 3 months without significant differences. However, more patients among those with CR after 90 days, who were followed up to 12 months, remained free of lesions, and fewer AKs recurred after cryotherapy. The thickness of the lesions influenced the therapeutic results: cryotherapy was more effective for grade III AKs after 3 months, and fewer grade II AKs recurred at 12 months after cryotherapy. A possible explanation is that cryotherapy provides for a more complete and uniform destruction of the epithelium than CO_2 laser.

The cosmetic outcome was rated good or excellent in the vast majority (approximately 90%) of patients with either treatment. The agreement between the scores given by the blinded investigator and the scores given by patients themselves was very good. Pain was moderate with cryotherapy, but the discomfort of local anaesthesia that was delivered before laser ablation must be taken into account and probably contributed to the higher overall patient satisfaction with cryotherapy. Some patients reported dissatisfaction with the time needed for wound healing after laser ablation. Finally, the analysis of cost-effectiveness per patient with CR and per lesion with CR favoured cryotherapy.

Although laser ablation and cryotherapy are suggested as valuable treatment options for isolated AKs in guidelines of scientific societies and expert consensus panels,[4,5,8–10] their relative efficiencies in the treatment of this subset of patients were not known.

Indeed, two studies, one retrospective[11] and the other prospective,[25] have previously investigated the therapeutic effects of cryotherapy, but the enrolled patients had a broad variation in the number of lesions, the treatment techniques were not standardized and the overall cure rates were very variable, ranging from 98·8% to 67·2%.[11,25]

In other studies, cryotherapy and laser ablation were compared with field-directed treatments such as photodynamic therapy (PDT) with methylaminolevulinate (MAL) cream,[14–17] or 5-aminolevulinic acid (5-ALA), imiquimod cream[18] and 5-fluorouracil cream[18] in the treatment of patients with multiple AKs.

The review of the above mentioned comparative studies with MAL-PDT shows that the cure rate of AKs 3–4 months after cryotherapy was 68%[15] with a single cycle of double freeze thaw, and 75%,[14] 86·1%[16] and 88%[17] with two cycles. In comparison with MAL-PDT, the efficacy of cryotherapy was similar[14,17] or higher,[15] if only a single treatment with MAL-PDT was delivered.[13] Cryotherapy was less efficient if two sessions of MAL-PDT were delivered to all patients[15] or only to lesions with an incomplete clearance after 12 weeks from a first treatment cycle.[16,17] In all studies, cosmetic outcome and patient preference favoured MAL-PDT.

The results of all these studies are not well comparable with the present findings. It is conceivable that the hazard of relapses and presentation of new lesions is higher for patients in whom multiple AKs, which are surrounded by clinically photodamaged skin, are treated with lesion-directed modalities.

In addition, several arguments can be put forward to explain, at least partially, why the cosmetic outcome with cryotherapy in those studies was worse in comparison with findings of this investigation. Firstly, severely photodamaged skin has a higher sensitivity to thermal injury and a lower reparative capacity[26] than normal or almost normal skin. Chronic actinic damage facilitates the development of scars and pigmentary changes following physical ablative treatments. These hazards likely increase with aggressive treatment protocols.[11,27] Indeed, all comparative studies of cryotherapy with MAL-PDT used one[15] or two[14,16,17] cycles of double freeze thaw that result in longer freezing time and more extensive damage to keratinocytes, melanocytes within hair follicles and the collagen matrix when compared with the cotton tip technique that was used herein.[11,27] Also, the type of medication after the treatment could influence the cosmetic outcome, but it was never described in detail in previous studies.[14–17] Furthermore, the cosmetic result with cryotherapy was assessed only 3[14] or 4[17] months after the treatment, but it is known that hypopigmentation and redness quite often improve in the following months.[20,21,28] Finally, MAL-PDT has the additional advantage of improving the overall appearance of the surrounding photoaged skin,[12,29] thus suggesting a more favourable evaluation of the cosmetic result.

Also, PDT with self-adhesive patches containing 8 mg of 5-ALA proved more effective and had a better cosmetic outcome than a single cycle of the open spraying procedure of cryotherapy for the treatment of patients with multiple mild (grades I and II) AKs of the face and scalp.[30,31]

Cryotherapy was less effective than 5% imiquimod cream (one to two treatment cycles with three weekly applications for 4 weeks) and 5% 5-fluorouracil cream (daily applications for 4 weeks): 68%, 96% and 85% of patients, respectively, achieved an initial clinical clearance after 2–3 months after concluding the treatment. At the 12-month follow-up examination 28%, 73% and 54%, respectively, had sustained clearance. The very low cure rate after cryotherapy may be caused to some extent by a nonaggressive freezing protocol.

The therapeutic effects of ablative CO_2 laser were investigated in only one previous randomized controlled study in comparison with MAL-PDT. Patients had multiple AKs and, therefore, MAL-PDT was more effective and delivered a better cosmetic result because of its additional general smoothing effect on the surrounding photodamaged skin.[12]

Finally, retrospective studies or studies with small case series investigated full face resurfacing with CO_2 laser or erbium: YAG laser for the treatment of multiple AKs and they reported variable results ranging from disappointing[32] to highly effective.[33–37] However, these results are not comparable with the present findings because the lasers were not used for ablation of single AKs.

In conclusion, we have found that under the conditions of the present investigation the efficacy, tolerability, cosmetic outcome and cost-effectiveness of both cryotherapy and laser ablation are high, with a preference for cryotherapy. Future studies on the biological activity of cryotherapy and laser ablation may help to optimize the treatment techniques, thus further improving outcomes. The comparative effectiveness of other treatment modalities remains to be clarified. Extrapolation of therapeutic results obtained in patients with multiple AKs needs to be viewed with caution.

An important current concern is the economic sustainability of health technologies within our healthcare systems. The widespread and potentially inappropriate use of expensive field-directed treatments for patients with isolated AKs may have serious economic consequences.

Indeed, from the perspective of the Italian Healthcare Service, a treatment course with MAL-PDT, imiquimod cream and diclofenac plus hyaluronic acid cream costs 320, 342 and 256 Euros, respectively, while the cost of both cryotherapy and ablative CO_2 laser is about 50 Euros.[38]

Therefore, at present, cryotherapy and CO_2 laser ablation should be considered first-line treatments for patients with isolated AKs. The use of other, field-directed therapies should be reserved for patients with multiple AKs with field cancerization, where higher efficacies and improved cosmetic outcomes of these modalities have been clearly demonstrated.

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