

# Treatments of actinic cheilitis: A systematic review of the literature



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**Background:** No large studies have defined the best treatment of actinic cheilitis.

**Methods:** We conducted a systematic review to define the best therapies for actinic cheilitis in clinical response and recurrences.

**Results:** We first identified 444 papers, and 49 were finally considered, including 789 patients and 843 treated areas. The following therapies were recorded in order of frequency: laser therapy, photodynamic therapy (PDT), 3% diclofenac in 2.5% hyaluronic acid, PDT + 5% imiquimod, aminolevulinic acid–laser or methyl-aminolevulinic acid–laser, 5% imiquimod, fluorouracil, partial surgery, 0.015% ingenol mebutate, 50% trichloroacetic acid, and laser + PDT. Concerning the primary outcome, complete clinical response was achieved in 76.5% of patients, and 10.2% had clinical recurrences. Partial surgery and laser therapy showed the highest complete response rates (14 of 14 [100%] and 244 of 260 [93.8%], respectively) with low recurrences. Only a limited number of patients were treated with other therapies, with the exception of PDT, with 68.9% complete responses and 12.6% of recurrences. Interestingly, when combined with 5% imiquimod, the efficacy of PDT was significantly enhanced.

**Limitations:** Heterogeneity across studies.

**Conclusion:** Laser therapy appears the best option among nonsurgical approaches for actinic cheilitis, and PDT showed higher efficacy when sequentially combined with 5% imiquimod. Larger studies are needed to confirm these data. (*J Am Acad Dermatol* 2020;83:876-87.)

**Key words:** actinic cheilitis; diclofenac; imiquimod; laser; photodynamic therapy; treatment.

Actinic cheilitis (AC) is a premalignant lesion with the potential to evolve into invasive squamous cell carcinoma (SCC). AC predominantly affects the lower lip of men aged older than 50 years and is clinically characterized by dryness, atrophy, scaling, focal erosions, and indistinct border.<sup>1-6</sup> On dermoscopic examination, AC shows white structureless areas, scales, white halos of the vermilion of the lip, and erosions.<sup>7,8</sup> AC has an estimated malignant transformation rate ranging from 10% to 30%.<sup>9</sup> Furthermore, literature data reported that 95% of SCCs of the lip originate from AC.<sup>10,11</sup> Thus, early diagnosis and treatment of AC are

of utmost importance to prevent development of SCC.

There is, however, no general consensus on the treatment of AC. Common treatment options include photodynamic therapy (PDT), cryosurgery, CO<sub>2</sub> laser ablation, electrodesiccation, and topical applications of fluorouracil (FU), 5% imiquimod (5% IMI), 3% diclofenac in 2.5% hyaluronic acid (DHA), and 0.015% ingenol mebutate (IngMeb). Several studies have compared the efficacy of AC treatments, but high-quality evidence to guide therapeutic decisions is still lacking.<sup>2,4,12,13</sup> The current study systematically reviewed the published literature to provide an

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overview of the efficacy of AC treatments in clinical response and, when available, histopathologic or dermoscopic clearance.

## METHODS

This systematic review followed the Meta-analysis of Observational Studies in Epidemiology guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines where feasible.<sup>14,15</sup>

### Search strategy

We performed a broad search in MEDLINE, Embase, and Cochrane Central Register of Controlled Trials electronic databases using the key words “actinic,” “solar,” “cheilitis,” and “cheilosis.” The search was performed from database inception until December 2018. The manual search was concluded by perusal of the reference sections of all relevant studies. Eligible studies were clinical trials, prospective studies, retrospective studies, case series, and case reports on humans written in English. Studies that did not report the results of AC treatment were excluded. Conventional surgical treatment was excluded because we aimed to focus our review on noninvasive approaches; thus, only partial surgical modalities were included, namely: dermabrasion, lip shave, and electrodesiccation with high energy. Cryotherapy was excluded because no papers primarily focused on this treatment modality.

### Data extraction

Two investigators (M.L. and L.C.) extracted data independently using a standardized extraction form. Any discordance was resolved by a third reviewer with experience in conducting systematic reviews and meta-analysis (R.P.). The following variables were collected: year, type of publication, study design, number of patients enrolled, age, sex, risk factors (eg, ultraviolet light and smoking), anatomic localization, extent, type of diagnosis (histologic or clinical), treatment, therapeutic scheme, response rate, type of response (clinical or histologic), healing time, duration of follow-up, recurrence rate, cosmetic outcome, and adverse events (AEs). Risk

of bias was classified for each of the included studies as low, moderate, and high, by the same investigators according to the PRISMA guidelines.

## Outcomes

The primary outcome was to evaluate the clinical response and recurrences of AC; if reported, even the dermoscopic and confocal results after treatment were considered. Secondary outcomes included the evaluation of the histopathologic response, AEs, and healing time.

## RESULTS

Fig 1 reports the flowchart. After removal of duplicates, 444 papers were identified. Of these, 372 were excluded on a title/abstract basis and 72 studies were selected. The study included 49 articles examining the treatment of AC, published from 1977 to 2018: 3 were case reports, 16 were case series, 10 were retrospective studies, and 20 were prospective studies.

We found high risk of bias levels for all the included studies.

### Demographics and clinical data

The 49 studies included 843 treated areas of 789 patients,<sup>8,16-63</sup> because in 2 studies, 54 patients were treated with 2 different therapies in 2 different areas, 40 were treated with 2 different CO<sub>2</sub> laser modalities and 14 with CO<sub>2</sub> laser and electrodesiccation with high energy.<sup>39,46</sup> Information on sex was recorded for 662 patients (42 studies),<sup>8,16-57</sup> 497 of whom were men (75.1%) with a mean age of 64.7 ± 9.5 years (range, 26-93 years) (38 articles, 613 patients).\*

The location of AC, registered in 582 patients enrolled in 38 studies,<sup>†</sup> was the lower lip in 566 (97.2%), upper lip in 6 (1.1%), and both lips in 10 (1.7%). Nine articles including 222 patients<sup>‡</sup> reported information on the percentage of the lip surface

## CAPSULE SUMMARY

- The estimated risk for actinic cheilitis to evolve into invasive squamous cell carcinoma ranges from 10% to 30%, which is significantly higher than for actinic keratosis on other body sites. Thus, early diagnosis and treatment of actinic cheilitis are of upmost importance to prevent progression to invasive squamous cell carcinoma.
- Our systematic review highlights that laser therapy can be considered the treatment with the highest clinical response, followed by 5% imiquimod and photodynamic therapy alone or combined. Further larger studies are warranted to confirm these data.

\*References 8, 16-45, 47, 49, 51, 52, 54-57.

†References 8, 17-19, 21-25, 28-30, 32-41, 43, 45-51, 53-60.

‡References 34-36, 39, 41, 45, 46, 48, 53.

**Abbreviations used:**

AC:	actinic cheilitis
AE:	adverse event
ALA:	aminolevulinic acid
DHA:	3% diclofenac in 2.5% hyaluronic acid
Er:YAG:	erbium-doped yttrium aluminium garnet laser
FU:	fluorouracil
IMI:	imiquimod
IngMeb:	ingenol mebutate
MAL:	methyl-aminolevulinic acid
PDT:	photodynamic therapy
SCC:	squamous cell carcinoma
TCA:	trichloroacetic acid

affected by AC: 55 had >75%, and 157 had between 50% and 75% involvement.

Information on risk factors for AC development were retrieved from 240 patients (33 studies).<sup>§</sup> Of these, 73 individuals had fair skin phenotype, 65 were smokers, 50 had history of nonmelanoma skin cancers or melanoma, 10 had a history of previous SCC of the lower lip, 37 were outdoor workers, 25 consumed alcohol, 5 reported intense recreational sun exposure, and 2 were immunosuppressed.

**Therapies for AC**

The review showed 789 patients, with 843 considered areas of the lips, were treated with the following therapies (Table 1): laser-therapy (335 [39.7%]),<sup>||</sup> PDT (257 [30.5%]),<sup>¶</sup> DHA (62 [7.4%]),<sup>16,18,34,43</sup> methyl-aminolevulinic acid (MAL) PDT + 5% IMI (34 [4.0%]),<sup>33</sup> MAL or aminolevulinic acid (ALA) plus laser (laser-PDT) (33 [3.9%]),<sup>26</sup> 5% IMI (30 [3.6%]),<sup>16,45,58</sup> FU (28 [3.3%]),<sup>50,55,60</sup> partial surgery (28 [3.3%]),<sup>46,50,59</sup> 0.015% IngMeb (25 [3.0%]),<sup>8,16,21,22,25</sup> 50% trichloroacetic acid (TCA) (10 [1.2%]),<sup>50</sup> and ALA-PDT plus excimer dye laser (1 [0.1%]).<sup>61</sup>

Of the included studies, 42 reported 1 treatment, including 576 patients in as many treated areas.<sup>#</sup> Of these, 238 patients, included in 17 studies, underwent PDT,<sup>\*\*</sup> 194 patients (11 studies) were treated with laser therapy,<sup>32,36,42,48-54,56</sup> 52 (3 studies) with DHA,<sup>18,34,43</sup> 34 (1 study) with MAL-PDT plus 5% IMI,<sup>33</sup> 20 (2 studies) with 5% IMI alone,<sup>45,58</sup> 18 (2 studies) with FU (12 with 5% FU and 6 with 1% FU),<sup>55,60</sup> 15 (4 studies) with 0.015% IngMeb,<sup>8,21,22,25</sup> 4 (1 study) with partial surgery (dermabrasion)<sup>59</sup> and 1 (1 study) with ALA-PDT plus excimer dye laser.<sup>40</sup>

Five studies,<sup>26,39,46,61,62</sup> including 197 treated areas of 143 patients, compared the efficacy of 2 treatments: 1 study (33 treated areas) compared laser-PDT (erbium-doped yttrium aluminium garnet [Er:YAG] laser and MAL-PDT) versus MAL-PDT alone,<sup>26</sup> 2 studies (115 treated areas) compared 2 different modalities of CO<sub>2</sub> laser,<sup>39,62</sup> 1 study (21 treated areas) compared dye laser versus laser + ALA-PDT,<sup>61</sup> and 1 study (28 treated areas) compared CO<sub>2</sub> laser versus electrodesiccation with high energy.<sup>46</sup> Only 1 study (30 patients/treated areas) compared the efficacy of 3 different treatments (5% IMI vs 0.015% IngMeb vs DHA)<sup>16</sup> and 1 (40 patients/treated areas) compared 4 different treatments (5% FU vs 50% TCA vs CO<sub>2</sub> laser vs lip shave).<sup>50</sup>

**Outcomes**

For outcome evaluation, it should be considered that all therapies included a limited number of patients with the exception for PDT and laser therapy. Moreover, outcomes were frequently assessed only on partial number of patients treated with each therapy.

**Clinical, dermoscopic response.** Of 49 studies reviewed, 45 reported 562 complete clinical responses on 735 treated areas (76.5%) evaluated.<sup>††</sup> Partial clinical responses were instead assessed in 21 of the 49 studies and were reported for 108 of 427 treated areas (25.3%). Poor response and the clinical worsening were only reported in a limited number of cases. The overall clinical recurrence rate, assessed in 30 studies,<sup>‡‡</sup> was 539 (10.2%) treated areas. Only 1 study evaluated dermoscopic and confocal responses, reporting 3 complete responses for patients with AC of the lower lip treated with 1 cycle of 0.015% IngMeb for 3 consecutive days.<sup>8</sup>

**Histopathologic response.** A post-therapy biopsy was only performed on 286 treated areas (34 studies including 470 treated areas).<sup>§§</sup> In 88.5% (253 of 286) of these cases, information on complete response was provided, with 160 (63.2%) achieving complete clearance.

**Adverse events.** Thirty-three articles reported information on AEs,<sup>||||</sup> with 1119 AEs registered on 582 patients (1.9 AEs per patient). The most commonly reported AEs included pain, erythema,

<sup>§</sup>References 8, 16-19, 22, 24-26, 32, 34-42, 44-48, 50-57, 61.

<sup>||</sup>References 32, 36, 39, 42, 46, 48-54, 56, 61-63.

<sup>¶</sup>References 17, 19, 20, 23, 24, 26-31, 35, 37, 38, 41, 44, 47, 57.

<sup>#</sup>References 8, 17-25, 27-38, 40-45, 47-49, 51-60, 63.

<sup>\*\*</sup>References 17, 19, 20, 23, 24, 27-31, 35, 37, 38, 41, 44, 47, 57.

<sup>††</sup>References 8, 16-29, 31-44, 45, 47, 48, 50-62.

<sup>‡‡</sup>References 8, 17-19, 21, 23, 24, 26-28, 31-37, 39, 44, 47, 48, 50, 51, 53-56, 59, 61, 62, 69.

<sup>§§</sup>References 8, 16, 17, 20, 23, 24, 26, 28, 30, 32, 33, 35, 37-48, 50, 52-54, 56-61.

<sup>||||</sup>References 8, 16, 17, 19, 20, 22, 23, 25, 26, 28-31, 33, 35-45, 47-49, 51, 56, 58, 59, 62.

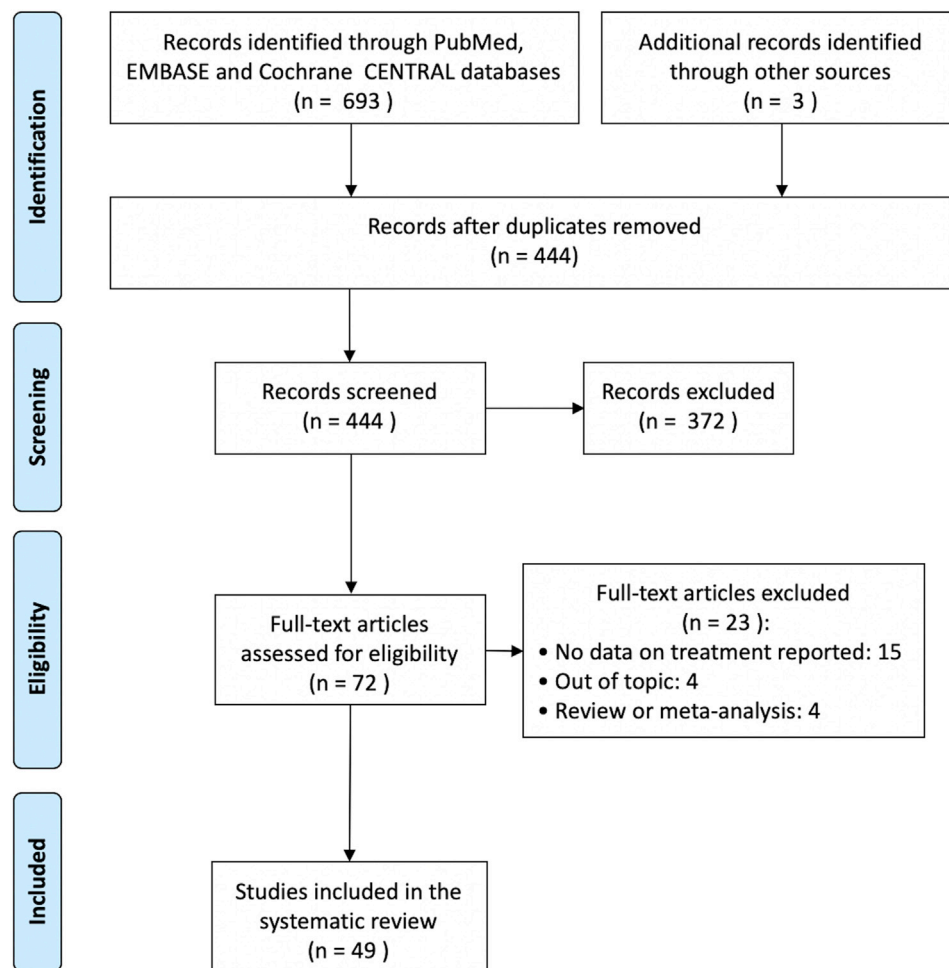


Fig 1. Flowchart of search results and study selection.

edema, and burning sensation. Almost all the scarring reactions were mild. In addition, 5 articles reported a mean visual analog scale pain value of  $5.7 \pm 1.9$  in 77 patients (65 treated with PDT and 12 with Er:YAG laser).<sup>30,35,37,42,44</sup> AEs resulted in 16 discontinuations reported in 7 studies (175 treated areas).<sup>18,25,29,33-35,50</sup>

**Cosmetic outcome.** Cosmetic outcome was evaluated in 11 studies<sup>11</sup> (181 treated areas), which was reported as excellent in 137 of 181 cases (75.7%).

**Healing time in different studies.** Seventeen articles,<sup>##</sup> including 303 treated areas, reported a mean healing time of 2.8 weeks (range, 0.4-4 weeks). The healing time was reported for 232 areas treated with CO<sub>2</sub> laser therapy, 16 treated with MAL-PDT, 5 with 5% IMI, 1 with 1% FU, 14 with electrodesiccation, 4 with dermabrasion, 19 with the

combination of dye laser and ALA-PDT, and 12 with Er:YAG laser.

### Outcomes according to each therapy

Table II, Table III, and Table IV report the analytic data for each specific treatment.

**Laser therapy.** All laser therapies, taken together, showed a 93.8% (244 of 260) complete clinical response rate, ranging from 93.5% (231 of 247) for CO<sub>2</sub> to 100% for both Er:YAG (12 of 12) and thulium (1 of 1) laser. Complete histopathologic response was reported in 73 of 76 cases (96.1%), and clinical recurrences were assessed in 14 of 235 cases (6.0%). The number of AEs per case was 0.4. Cosmetic outcome was reported as excellent in 36 of 36 areas evaluated.

**Laser + photodynamic therapy.** Only 1 patient was treated with laser + PDT, experiencing complete clinical and histopathologic clearance.

**Partial surgery.** Partial surgery showed the highest rate of complete response (14 of 14 [100%]), and no recurrences were reported. Complete histopathologic response was registered in 10 of 12

<sup>11</sup>References 19, 29, 31, 35, 37, 38, 43, 47, 52, 54, 56.

<sup>##</sup>References 20, 39, 42, 46, 48, 49, 51-54, 56, 58-63.

**Table I.** Therapies for actinic cheilitis

Treatment category	No. of studies	No. of patients (treated areas, if different in No.); mean age $\pm$ SD (range); M/F	Therapy	No. of cycles and schedule	Days of effective therapy	Follow up (mo)		
						No. of studies	No. of patients	Mean (range)
Partial surgery <sup>46,50,59</sup>	3	28 (42)	Electrodessication with high energy (1 study, 14 patients, 28 treated areas) <sup>46</sup> Lip shave (1 study, 10 patients) <sup>50</sup> Dermabrasion (1 study, 4 patients) <sup>59</sup>	1	1	3	28	NR (3.0-48.0)
Laser + PDT (excimer dye + ALA) <sup>40</sup>	1	1; 67.0; M/F: 0/1	ALAL-PDT + excimer dye laser 630 nm	1	1			
Laser*	16	295 (335); 60.1 $\pm$ 11.0 (26-93); M/F: 192/40	CO <sub>2</sub> (13 studies, 293 patients, 333 treated areas) <sup>†</sup> Er:YAG (1 study, 12 patients) <sup>42</sup> 1.927-nm thulium (1 study, 1 patient) <sup>32</sup> Dye 595 nm (1 study, 2 patients) <sup>61</sup>	1 to 3 (292 patients did 1; 1 patient treated with CO <sub>2</sub> laser did 2 at 1.5-month interval, 2 patients treated with thulium and dye laser did 3 at monthly interval)	1 to 3	10	205	21.7 (1.3-60.0)
MAL PDT + 5% IMI <sup>33</sup>	1	34; 65.3 $\pm$ 6.2 (54-78); M/F: 33/1	MAL-PDT + 5% IMI	2 sessions of MAL-PDT at 2-week interval then 1 cycle of 5% IMI 3 days/week for 4 weeks	14	1	34	12.0 (12.0-12.0)
Laser-PDT <sup>26,61</sup>	2	33; 66.7 $\pm$ 8.7 (42-86); M/F: 9/5	ALA-dye 595 (1 study, 19 patients) <sup>61</sup> MAL-Er:YAG (1 study, 14 patients) <sup>26</sup>	1 to 3 at monthly interval	1 to 3	2	33	7.5 (1.0-12.0)
FU <sup>50,55,60</sup>	3	28; 55.6 $\pm$ 11.1 (36-73); M/F: 8/4	5% FU in 2 studies (22 patients) <sup>50,55</sup> 1% FU in 1 study (6 patients) <sup>60</sup>	1 (3 times a day) 1 (twice a day)	12-21	3	28	22.0 (2.0-48.0)

5% IMI <sup>16,45,58</sup>	3	30; 68.6 ± 1.4 (41-85); M/F: 16/9	5% IMI	1 (25 patients 3 times a week for 4-6 weeks; 5 patients 5 consecutive days per week for 6 weeks)	12-30	3	20	NR (1.0-18.0)
PDT <sup>‡</sup>	18	257; 67.5 ± 9.6 (26-90); M/F: 177/807	PDT overall	1-6 (mean: 2) at 1- to 12-week interval (mean: 1.5)	1-6	18	257	11.1 (2.0-60.0)
			MAOP (2 studies, 18 patients) <sup>41,44</sup>	2 (mean: 2) at 1-week interval (mean: 1)	2	2	18	5.5 (4.0-13.0)
			Alacare <sup>§</sup> patch (1 study, 11 patients) <sup>19</sup>	1-2 (mean: 1.7) at 2-week interval (mean: 1.5)	1-2	1	11	12.0 (12.0-12.0)
			ALA (3 studies, 51 patients) <sup>35,38,47</sup>	1-3 (mean: 2) at 1- to 12-week interval (mean: 2)	1-3	3	51	14.4 (3.0-18.0)
			MAL (9 studies, 154 patients) <sup>  </sup>	1-6 (mean: 2) at 1- to 4-week interval (mean: 1.2)	1-6	9	154	9.2 (2.0-30.0)
			MAL daylight (3 studies, 23 patients) <sup>17,24,28</sup>	1-6 (mean: 2.5) at 1- to 4-week interval (mean: 2.2)	1-6	3	23	20.5 (4.0-60.0)
0.015% IngMeb <sup>8,16,21,22,25</sup>	5	25; 76.0 ± 1.4 (54-90); M/F: 14/11	0.015% IngMeb	1, only 1 patient did 2 (3 consecutive days)	3-6	5	25	5.2 (1.0-10.0)
DHA <sup>16,18,34,43</sup>	4	62; 61.8 ± 10.2 (38-82); M/F: 48/14	DHA	1 (5 patients once daily for 42 days; 38 patients twice daily for 30-180 days; 19 patients 3 times a day for 90 days)	30-180	4	62	87 (15-12.0)
50% TCA <sup>50</sup>	1	10; NA (52-67); M/F: NA	50% TCA	1	1	1	10	NR (NR-34.0)

Continued



Table I. Cont'd

Treatment category	No. of studies	No. of patients (treated areas, if different in No.); mean age $\pm$ SD (range); M/F	Therapy	No. of cycles and schedule	Days of effective therapy	No. of studies	No. of patients	Follow up (mo)	
								Mean	(range)
Overall	49	789 (834); 64.7 $\pm$ 9.5 (26-93); M/F: 497/161		1-6	1-180	42	688	13.2	(1.0-60.0)

ALA, Aminolevulinic acid; DHA, 3% diclofenac in 2.5% hyaluronic acid; Er:YAG, erbium-doped yttrium aluminium garnet laser; F, female; FU, fluorouracil; IMI, imiquimod; IngMeB, ingenol mebutate; M, male; MAL, methyl-aminolevulinic acid; MAOP, methyl-aminoxopentanoate; NA, not available; NR, not reported; PDT, photodynamic therapy; TCA, trichloroacetic acid.

\*References 32, 36, 39, 42, 46, 48-54, 56, 61-63.

†References 36, 39, 46, 48-54, 56, 62, 63.

‡References 17, 19, 20, 23, 24, 26-31, 35, 37, 38, 41, 44, 47, 57.

§Photonic GmbH, Wedel, Germany.

||References 20, 23, 26, 27, 29-31, 37, 57.

evaluated cases (83.3%). The number of AEs per case was 0.3.

**MAL-PDT + 5% imiquimod.** A complete clinical response rate of 79.4% (27 of 34) was calculated for MAL-PDT + 5% IMI, and complete histopathologic response was 64.7% (22 of 34). Clinical recurrences were reported in 2 of 34 cases (5.9%). The number of AEs per case was 5.4, with discontinuation for AEs in 5.9%.

**Laser-photodynamic therapy.** Complete clinical response was reported in 25 of 33 cases (75.8%), ranging from 68.4% for ALA PDT-dye laser to 85.7% for MAL PDT-Er:YAG laser. Histopathologic response was not reported. Clinical recurrences were assessed in 6.1% (2 of 33) of cases.

**Fluorouracil.** Complete clinical response was achieved in 75.0% (21 of 28) of cases (68.2% for 5% FU and 100% for 1% FU). The recurrence rate was 31.8% (7 of 22). Concerning histopathologic response, 5 of 6 cases experienced partial clearance and 1 of 6 poor response. Discontinuation for AEs was reported in 10.0% of cases.

**5% imiquimod.** Complete clinical response was reported in 73.3% (22 of 30) of cases, whereas only 2 of 5 evaluated cases achieved complete histopathologic response. The number of AEs per case was 3.1.

**Photodynamic therapy.** The complete clinical response rate for PDT was 68.9% (164 of 238). The highest ratio was reached with the MAL daylight approach (82.6%), whereas methyl-aminoxopentanoate-PDT showed the worst performance (55.6%). ALA-PDT performed better than MAL-PDT (74.5% vs 65.9% complete response rate). Clinical recurrences were reported in 19 of 151 cases (12.6%). Complete histopathologic response was assessed in 42.5% (48 of 113) of cases, with ALA-PDT showing higher performance than MAL-PDT (52.1% and 24.4%, respectively). The number of AEs per case was 2.4, and discontinuation for AEs was reported in 6.2%. Cosmetic outcome was judged to be excellent in 95 of 139 cases (68.3%).

**0.015% ingenol mebutate.** The complete response rate was 52.0% (13 of 25), and recurrences were reported in 1 of 4 cases (25.0%). Number of AEs per case was 4.0, and discontinuations for AEs happened in 1 of 4 cases (25%).

**Diclofenac in 2.5% hyaluronic acid.** A 45.2% (28 of 62) complete clinical response rate was reported, and complete histopathologic response occurred in 66.7% (4 of 6) of evaluated cases. Clinical recurrences were found in 6.5% (3 of 46) of cases. Cosmetic outcome was considered to be excellent in 6 of 6 cases. Discontinuations for AEs was reported in 15.2%.

**50% trichloroacetic acid.** Only 3 of 10 areas treated with 50% TCA had complete clinical clearance.

**Table II.** Clinical response and recurrences according to therapy

Clinical response Articles	Complete		Partial		Poor		Worsening		Recurrences	
	45		21		3		5		30	
Therapies	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
Partial surgery <sup>46,50,59</sup>	14/14	100.0	NR	NR	NR	NR	1/14	7.1	0/4	0.0
Laser + PDT (excimer dye + ALA) <sup>40</sup>	1/1	100.0	NR	NR	NR	NR	NR	NR	NR	NR
Laser overall	244/260	93.8	10/80	12.5	NR	NR	5/100	5.0	14/235	6.0
Laser CO <sub>2</sub> *	231/247	93.5	10/80	12.5	NR	NR	5/100	5.0	14/234	6.0
Laser Er:YAG <sup>42</sup>	12/12	100.0	NR	NR	NR	NR	NR	NR	NR	NR
Laser thulium <sup>32</sup>	1/1	100.0	NR	NR	NR	NR	NR	NR	0/1	0.0
MAL PDT + 5% IMI <sup>33</sup>	27/34	79.4	3/34	8.8	NR	NR	NR	NR	2/34	5.9
Laser-PDT overall	25/33	75.8	2/19	10.5	NR	NR	NR	NR	2/33	6.1
Laser-PDT ALA-dye <sup>61</sup>	13/19	68.4	2/19	10.5	NR	NR	NR	NR	1/19	5.3
Laser-PDT MAL-Er:YAG <sup>26</sup>	12/14	85.7	NR	NR	NR	NR	NR	NR	1/14	7.1
FU overall	21/28	75.0	NR	NR	NR	NR	NR	NR	7/22	31.8
FU 0.05 <sup>50,55</sup>	15/22	68.2	NR	NR	NR	NR	NR	NR	7/22	31.8
FU 0.01 <sup>60</sup>	6/6	100.0	NR	NR	NR	NR	NR	NR	NR	NR
5% IMI <sup>16,45,58</sup>	22/30	73.3	7/15	46.7	1/10	10.0	NR	NR	NR	NR
PDT overall	164/238	68.9	54/196	27.6	6/72	8.3	1/29	3.5	19/151	12.6
PDT MAOP <sup>41,44</sup>	10/18	55.6	7/15	46.7	NR	NR	NR	NR	0/3	0.0
PDT ALA patch <sup>19</sup>	8/11	72.7	2/11	18.2	NR	NR	NR	NR	2/11	18.2
PDT ALA <sup>35,38,47</sup>	38/51	74.5	14/51	27.5	NR	NR	NR	NR	4/41	9.8
PDT MAL <sup>†</sup>	89/135	65.9	30/108	27.8	6/72	8.3	1/29	3.5	10/73	13.7
PDT MAL daylight <sup>17,24,28</sup>	19/23	82.6	1/11	9.1	NR	NR	NR	NR	3/23	13.0
0.015% IngMeb <sup>8,16,21,22,25</sup>	13/25	52.0	8/21	38.1	3/10	30.0	NR	NR	1/4	25.0
DHA <sup>16,18,34,43</sup>	28/62	45.2	24/62	38.7	4/10	40.0	1/19	5.3	3/46	6.5
50% TCA <sup>50</sup>	3/10	30.0	NR	NR	NR	NR	NR	NR	7/10	70.0
Overall	562/735	76.5	108/427	25.3	14/102	13.7	8/162	4.9	55/539	10.2

ALA, Aminolevulinic acid; DHA, 3% diclofenac in 2.5% hyaluronic acid; Er:YAG, erbium-doped yttrium aluminium garnet laser; FU, fluorouracil; IMI, imiquimod; IngMeb, ingenol mebutate; MAL, methyl-aminolevulinic acid; MAOP, methyl-aminoxopentanoate; NR, not reported; PDT, photodynamic therapy; TCA, trichloroacetic acid.

\*References 36, 39, 46, 48-54, 56, 62, 63.

†References 20, 23, 26, 27, 29, 30, 31, 37, 57.

## DISCUSSION

The current systematic review demonstrated that the highest complete response rates were reported for partial surgery and laser therapy, alone or combined with PDT, followed by MAL-PDT + 5% IMI, FU, and PDT alone. However, most of the considered therapies only accounted for a small number of cases, and the absolute number of areas treated with each therapy should be considered when comparing results. In particular, only laser therapy and PDT included >200 cases each, whereas 62 areas were treated with DHA. Laser therapy appeared to be the best approach, with 93.8% of complete response and only 5.0% of clinical worsening and 6.0% of recurrences. Most of the patients were treated with CO<sub>2</sub> laser; thus, our results mainly refer to this modality. PDT showed relatively low levels of complete response (68.9%) compared with other therapies such as laser therapy, FU, and 5% IMI; moreover, the response was

poor in 8.3% of cases, and 12.6% experienced a clinical recurrence. Finally, DHA showed a very low level of complete response (45.2%) and the highest poor response (40.0%); while recurrences occurred in 6.5% of cases.

Taken together, our results support the efficacy of CO<sub>2</sub> laser therapy for AC. This finding is consistent with the National Comprehensive Cancer Network Guidelines for Squamous Cell Skin Cancer that consider ablative laser vermilionectomy to be a valuable therapeutic option for extensive AC.<sup>64</sup> Conversely, European and British guidelines for the treatment of actinic keratosis do not cover AC management.<sup>65</sup> However, PDT and DHA seem to be less effective. This may be explained by the fact that PDT and DHA are both influenced by the presence of crusts and patient compliance.

Results concerning the other therapies should be interpreted with caution because a low number of patients were treated. In general, the sequential use



**Table III.** Histologic response and recurrences according to therapy

Histologic response Articles	Complete		Partial		Poor		Worsening		Recurrences	
	19		11		3		2		4	
Therapies	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
Partial surgery <sup>46,50</sup>	10/12	83.3	2/2	100.0	NR	NR	NR	NR	NR	NR
Laser + PDT (excimer dye + ALA) <sup>40</sup>	1/1	100.0	NR	NR	NR	NR	NR	NR	NR	NR
Laser overall	73/76	96.1	2/5	40.0	NR	NR	NR	NR	0/14	0.0
Laser CO <sub>2</sub> <sup>39,46,48,50,53,56</sup>	73/76	96.1	2/5	40.0	NR	NR	NR	NR	0/14	0.0
Laser Er:YAG <sup>42</sup>	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Laser thulium <sup>32</sup>	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
MAL PDT + 5% IMI <sup>33</sup>	22/34	64.7	3/34	8.8	NR	NR	NR	NR	3/34	8.8
Laser-PDT overall	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Laser-PDT ALA-dye <sup>61</sup>	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Laser-PDT MAL-Er:YAG <sup>26</sup>	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
FU overall	0/6	0.0	5/6	83.3	1/6	16.7	NR	NR	NR	NR
FU 0.05 <sup>50,55</sup>	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
FU 0.01 <sup>60</sup>	0/6	0.0	5/6	83.3	1/6	16.7	NR	NR	NR	NR
5% IMI <sup>58</sup>	2/5	40.0	3/5	60.0	NR	NR	NR	NR	NR	NR
PDT overall	48/113	42.5	36/101	35.6	9/21	42.9	6/21	28.6	10/43	23.3
PDT MAOP <sup>41</sup>	5/13	38.5	8/13	61.5	NR	NR	NR	NR	NR	NR
PDT ALA patch <sup>19</sup>	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
PDT ALA <sup>35,38</sup>	25/48	52.1	14/48	29.2	NR	NR	NR	NR	9/38	23.7
PDT MAL <sup>20,23,30</sup>	11/45	24.4	14/35	40.0	9/16	56.3	6/16	37.5	NR	NR
PDT MAL daylight <sup>17,28</sup>	7/7	100.0	0/5	0.0	0/5	0.0	0/5	0.0	1/5	20.0
0.015% IngMeb <sup>16,45,58</sup>	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
DHA <sup>34,43</sup>	4/6	66.7	2/6	33.3	NR	NR	NR	NR	NR	NR
50% TCA <sup>50</sup>	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Overall	160/253	63.2	53/159	33.3	10/27	37.0	6/21	28.6	13/91	14.3

ALA, Aminolevulinic acid; DHA, 3% diclofenac in 2.5% hyaluronic acid; Er:YAG, erbium-doped yttrium aluminium garnet laser; FU, fluorouracil; IMI, imiquimod; IngMeb, ingenol mebutate; MAL, methyl-aminolevulinic acid; MAOP, methyl-aminoxopentanoate; NR, not reported; PDT, photodynamic therapy; TCA, trichloroacetic acid.

of 2 different therapies seems to synergistically increase the efficacy of each therapy considered alone. Notably, when combining MAL-PDT + 5% IMI a 79.4% complete response was achieved, whereas the levels of complete response were 73.3% for 5% IMI and 65.9% for MAL-PDT alone. The highest efficacy of PDT + IMI may be explained by their different mechanisms of action, with a selective destruction of neoplastic cells produced by PDT and a subsequent enhancement of the immune response produced by IMI.

Literature data suggest that sequential treatment of patients with PDT and 5% IMI is associated with better clinical and histologic response rate than PDT alone.<sup>33</sup> On one hand, PDT involves the activation of a photosensitizing drug by visible light, leading to production of reactive oxygen species within target cells and resulting in their destruction. On the other hand, IMI is an immune response modifier that acts as a Toll-like receptor agonist that stimulates the production of proinflammatory cytokines, which consecutively induces a tumor-directed cellular immune

response. Sotiriou et al<sup>33</sup> speculated that post-PDT inflammation may facilitate the IMI-induced activation of innate immunity, promoting the recruitment of activated effector cells into the tumor tissue.<sup>33</sup> In addition, the lack of standardized definitions of histologic response and the post-treatment biopsies at different time intervals in distinct lip sites make correlation with the clinical response not feasible. Most treatments for AC were well tolerated, with few AEs and excellent cosmetic outcomes.

Limitations of our review include the small sample sizes of most of the published studies and the significant heterogeneity in the quality and type of presented data, precluding comparisons. This review may also be affected by a bias toward reporting series with positive outcomes, because negative and equivocal results of AC treatments may not have been published. Histopathologic response and follow-up timing were highly variable among studies. Furthermore, none of the studies evaluated the use of cryotherapy for AC, which indeed is commonly used in clinical practice.

**Table IV.** Adverse events, cosmetic outcome, and healing time according to therapy

Outcomes	Adverse events (AEs)												AEs total		AEs discontinuation		Cosmetic outcome excellent		Healing time
	Articles												33		7 <sup>18,25,29,33,34,35,50</sup>		11 <sup>†</sup>		17 <sup>‡</sup>
Therapies	Pain	Erythema	Crusting	Inflammatory reaction	Flaking	Pustules, vesicles, blisters	Erosion, ulceration, bleeding	Swelling, edema	Burning sensation	Itch, dysesthesias, paresthesias	Scarring	Outbreak of herpes/ infection	n/N	N of AEs per case	n/N	%	n/N	%	Mean (range)
Partial surgery <sup>46,50,59</sup>	0	0	0	0	0	0	0	0	0	0	1	0	1/4	0.3	NR	NR	NR	NR	3.0 (2.0-3.3)
Laser + PDT (excimer dye + ALA) <sup>40</sup>	1	0	0	0	0	0	0	0	0	0	0	0	1/1	1.0	NR	NR	NR	NR	NR
Laser overall	24	0	0	0	0	0	8	10	1	6	38	2	89/225	0.4	NR	NR	36/36	100.0	3.0 (2.0-4.0)
Laser CO <sub>2</sub> <sup>3</sup>													59/213	0.3	NR	NR	36/36	100.0	NR
Laser Er:YAG <sup>42</sup>													30/12	2.5	NR	NR	NR	NR	NR
Laser Thulium													NR	NR	NR	NR	NR	NR	NR
MAL PDT+5% IMI <sup>33</sup>	30	30	25	0	25	6	0	24	30	14	0	0	184/34	5.4	2/34	5.9	NR	NR	NR
Laser-PDT overall	0	13	3	0	0	0	2	5	13	0	0	0	36/14	2.6	NR	NR	NR	NR	0.4 (0.4-0.4)
Laser-PDT ALA-dye <sup>26,61</sup>													NR	NR	NR	NR	NR	NR	NR
Laser-PDT MAL-Er:YAG													36/14	2.6	NR	NR	NR	NR	NR
FU overall	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	1/10	10.0	NR	NR	4.0 (4.0-4.0)
FU 0.05 <sup>50,60</sup>													NR	NR	1/10	10.0	NR	NR	NR
FU 0.01													NR	NR	NR	NR	NR	NR	NR
5% IMI <sup>16,45,58</sup>	5	19	10	15	0	0	14	19	10	0	0	0	92/30	3.1	NR	NR	NR	NR	4.0 (4.0-4.0)
PDT overall	162	132	33	29	17	16	17	85	72	0	1	6	570/234	2.4	5/81	6.2	95/139	68.3	2.0 (2.0-2.0)
PDT MAOP <sup>41,44</sup>													46/18	2.6	NR	NR	NR	NR	NR
PDT ALA patch <sup>19</sup>													16/11	1.5	NR	NR	8/11	72.7	NR
PDT ALA <sup>35,38,47</sup>													182/51	3.6	0/38	0.0	27/51	52.9	NR
PDT MAL <sup>20,23,26,29-31,37</sup>													305/141	2.2	5/43	11.6	60/77	77.9	NR
PDT MAL daylight <sup>17,28</sup>													21/13	1.6	NR	NR	NR	NR	NR
0.015% IngMeb <sup>8,16,22,25</sup>	0	22	18	0	10	7	8	21	10	0	0	0	96/24	4.0	1/4	25.0	NR	NR	NR
DHA <sup>16,18,34,43</sup>	0	14	10	0	0	0	0	16	10	0	0	0	50/16	3.1	7/46	15.2	6/6	100.0	NR
50% TCA <sup>50</sup>	0	0	0	0	0	0	0	0	0	0	0	0	NR	NR	NR	NR	NR	NR	NR
Overall	222	230	99	44	52	29	49	180	146	20	40	8	1119/582	1.9	16/175	9.1	137/181	75.7	2.8 (0.4-4.0)

AEs, Adverse events; ALA, aminolevulinic acid; DHA, 3% diclofenac in 2.5% hyaluronic acid; Er:YAG, erbium-doped yttrium aluminium garnet laser; FU, fluorouracil; IMI, imiquimod; IngMeb, ingenol mebutate; MAL, methyl-aminolevulinic acid; MAOP, methyl-aminoxopentanoate; NR, not reported; PDT, photodynamic therapy; TCA, trichloroacetic acid.

\*References 8, 16, 17, 19, 20, 22, 23, 25, 26, 28-31, 33, 35-45, 47-49, 51, 56, 58, 59, 62.

†References 19, 29, 31, 35, 37, 38, 43, 47, 52, 54, 56.

‡References 20, 39, 42, 46, 48, 49, 51-54, 56, 58-63.

§References 36, 39, 46, 48, 49, 51-54, 56, 60, 62, 63.

**CONCLUSION**

The current study compiles available data on AC treatments and can respond to an unmet need. We found that evidence of efficacy was very low quality for all of the interventions considered, and although there is insufficient evidence to recommend any particular treatment, laser therapy alone or combined with PDT can be considered the treatment with the highest clinical response, followed by FU and 5% IMI and PDT alone or combined. Larger studies, especially randomized controlled studies, are needed to further evaluate the efficacy and safety of the commonly used treatments for AC to assess the optimal therapeutic strategy for these patients.

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