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Concomitant Use of Isotretinoin and Lasers with Implications for Future Guidelines: An Updated Systematic Review

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Manuscript Word Count: 2664 **Figure(s):** 0 **Table(s):** 3

Abstract Word Count: 184 **Reference(s):** 41 **Supplement(s):** *Fig* 1 *Tab 2*

Key Points

Question. Is the concomitant use of isotretinoin and lasers on the skin safe and/or effective?

Findings. This systematic review revealed that the rate of adverse events in patients with concomitant use is low, and that when adverse events do occur, these are often transient and resolve spontaneously.

Meaning. Considering the low rate of adverse events and high satisfaction with concomitant use of isotretinoin and lasers, further studies are needed to determine whether current guidelines highlighting contraindication are appropriate.

Author Contributions: Mirza, Mirza had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Mirza, Mirza, Khatri. *Acquisition, analysis, or interpretation of data:* Mirza, Mirza. *Drafting of manuscript:* Mirza, Mirza. *Critical revision of manuscript for important intellectual content:* Khatri. *Statistical Analysis:* N/A. *Obtained Funding:* N/A. *Administrative, technical, or material support:* Mirza, Mirza, Khatri. *Study supervision:* Khatri.

Funding/Support: This systematic review was conducted without financial support.

Role of the Sponsors:

	Funding/Sponsor was Involved?
Design and conduct of study	No
Collection, management, analysis, and interpretation of data	No
Preparation, review, or approval of the manuscript	No
Decision to submit the manuscript for publication	No

Financial Disclosure : None reported.

All Financial Interests (including pharmaceutical and device products): None reported.

Acknowledgement: N/A.

Abstract

Background. It is generally believed that intervention on skin while on isotretinoin or within 6-12 months after treatment can lead to prolonged healing and abnormal scarring.

Objective. The objective of this systematic review is to evaluate the body of evidence on concomitant use of isotretinoin and lasers for adverse events as a consequence of treatment.

Methods & Materials A PRISMA-compliant systematic review (Systematic Review Registration Number: CRD42017056492) of twelve electronic databases was conducted for the terms 'laser' and 'isotretinoin' or associated brand names from inception until June 2020. Subsequent reference search of studies meeting predefined inclusion criteria were conducted, and all articles were evaluated for bias and assigned levels of evidence to facilitate data synthesis.

Results. The search strategy produced 29 studies. Of 871 patients included in the studies of interest, twelve experienced transient adverse effects that resolved spontaneously, and only two presented with keloid formation, both from case reports.

Conclusions. This systematic review suggests the risk associated with concomitant isotretinoin and laser use is small to absent. Further studies are needed, but these results suggest that current contraindications may be overly cautious.

Keywords: isotretinoin, lasers, concomitant treatment, systematic review, safe and effective

Introduction

The American Academy of Dermatology guidelines recommends delaying laser resurfacing 6-12 months after discontinuing isotretinoin, citing early case series describing delayed wound healing in patients with concomitant use. Current recommendations rely heavily on case reports published over three decades ago.

Acne is the most common skin condition in the United States, affecting up to 50 million American annually.(Bickers *et al.*, 2006) A subset of these patients suffer from severe inflammatory acne, often presenting with severe acne scars. There is evidence that early intervention results in better outcomes (Fitzpatrick, 1999; Lupton and Alster, 2002).

Therefore, it is important to consider the impact on the patient when requesting delay of laser treatment due to guidelines developed from multiple-decade old case reports.

In 2017, two consensus statements considered several procedural interventions in the setting of isotretinoin, challenging the common practice of a latency period between systemic isotretinoin therapy and other treatments. Since that time, several additional studies have been published with no systematic review considering the adverse consequences of concomitant laser and isotretinoin. Furthermore, these studies did not report the efficacy, frequency, nor dosage of the lasers; important metrics for understanding limitations of practical laser use in this context. Our aim was to conduct a systematic review that may inform evidence-based guidelines and shape clinic practice for the benefit of the patient, focusing specifically on laser use.

Methods

The protocol was registered on International Prospective Register of Systematic Reviews, and adheres to the principles of the PRISMA guidelines(Moher *et al.*, 2009) (CRD42017056492) .

Search Strategy & Study Selection

We searched twelve databases for any published studies through June 2020 with the search strategy: ((laser* OR photodynamic*)) AND (Isotretinoin OR Accutane OR Roaccutane OR Amnesteem OR Claravis OR Absorica OR Isotroin OR Epuris)[all]. No language restriction was applied, and inclusion/exclusion criteria were assessed (supplemental table 1). We checked the bibliographies further potentially eligible studies. We used the Oxford Center for Evidence-Based Medicine Levels of Evidence(Howick *et al.*, 2011) to assign the appropriate value to facilitate data synthesis.

Quality Assessment

The Cochrane Methods Bias Group's Risk of Bias in Non-Randomized Studies – of Interventions (ROBINS-I) Tool(Sterne *et al.*, 2016) was used to assess risk of bias in studies by two review authors, with disagreements resolved by a third author (supplemental table 2).

Data Synthesis

Two researchers extracted data. The outcomes related to the review question considered the efficacy (e.g. cosmetic improvement) or adverse events (e.g. scarring, keloids) associated with concomitant use, and if a control group was provided, the comparison of these outcomes between groups.

Results

After an iterative process of cross referencing, 29 studies met the inclusion criteria (supplemental figure 1).

The 29 retrieved studies include one expert opinion, eight case reports, eleven uncontrolled open-label trials, and eight controlled open-label trial, and included an aggregate of 871 patients (table 1).

Controlled open-label trials

One study considered the difference between patients undergoing isotretinoin and laser treatment with patients on prescription alone. Moradi et al(Moradi *et al.*, 2009) enrolled 148 patients for laser resurfacing on oral isotretinoin for acne scarring. The intervention arm was treated with three Nlite and five weekly Er: YAG sessions whereas the age-matched control group received isotretinoin alone. At six months post-treatment, rates of post-inflammatory hyperpigmentation were the same between groups at 3%.

Two studies used a split-face model. Saluja et al(Saluja *et al.*, 2017) and Xia et al(Xia *et al.*, 2018) conducted a randomized split-face control trail on 10 and 18 patients, respectively, for acne or acne with treatments with an erbium-doped laser. Patients showed improvement in

scarring without adverse effects, and for the latter, significantly improved comedo lesions on the non-ablative fractional laser (NAFL)-treated half-faces.

Five studies subjected all patients to laser treatment and compared a group with concomitant isotretinoin use with a control group not on isotretinoin. Leal and Cantu(Leal and Cantu, 2011) treated 60 patients for acne scarring with fractionated erbium laser on and off low-dose of isotretinoin; no difference or variation on the erythema, edema, and scabbing in the recovery process was observed. Kim et al(Kim *et al.*, 2014) evaluated 20 patients on fractional ablative carbon dioxide laser treatment with moderate to much improved cosmetic scores, and erythema and crust associated with laser treatment in both groups resolved in all patients within one month. Chandrashekar et al(Chandrashekar *et al.*, 2014) compared 60 patients treated with either carbon dioxide or 980 nm diode on isotretinoin (0.5 mg kg^{-1}); roughly 8% of those treated with carbon dioxide laser experienced hyperpigmentation that resolved within two months, and all report excellent results. Yoon et al(Yoon *et al.*, 2014) enrolled 35 participants who underwent acne scar revision with a 1550 nm erbium-doped laser, where 94% of the concomitant group showed improvement versus 88% of the control. No adverse events were reported. Kim et al(Kim *et al.*, 2020) demonstrated the safe use of CO_2 laser therapy and fractional microneedle radiofrequency for acne and acne scarring in 43 patients compared to 28 patients not on isotretinoin. Those on concomitant treatment had improved scar global assessment scores, and no persistent side effects were observed.

Uncontrolled open-label trials

Five studies focused on laser hair removal, four on acne scar revision, and three on a combination or other.

Khatri 2004(Khatri, 2004) reported 810 nm diode laser hair removal on the axilla, bikini, and chin in seven female patients, and one-month post-treatment, no scarring was found. One patient developed a transient bulla that resolved spontaneously within one month. Cassano et al(Cassano, Arpaia and Vena, 2005) presented six women undergoing laser hair removal on the face, where one patient presented with a sparse dotted crusting that healed spontaneously within a few days. Khatri and Garcia(Khatri and Garcia, 2006) described six female patients with satisfactory hair removal and no scarring during the six month follow-up. Khatri 2009(Khatri, 2009) reviewed eleven patients who underwent laser hair with a 1064 nm Nd:YAG laser where one patient experienced transient hyperpigmentation that resolved within three months. This rate of complications was not higher than that observed with patients taking isotretinoin alone.

Hann et al(Hann *et al.*, 2010) used a 1550 nm infrared fractional laser to treat acne scarring in 35 patients. Using a five-point cosmetic scale, over 80% of patients demonstrated moderate to excellent improvement, and no hypertrophic scarring or keloids were found. Jeong et

al(Jeong *et al.*, 2013) treated 20 patients on isotretinoin with a single session of full-face ablative fractional carbon dioxide laser. At four-year follow-up, and acne scar revision was deemed satisfactory. Khatri et al 2015(Khatri, Iqbal and Bhawan, 2015) tested three sites on a 19-year-old man's lower back with a nonablative fractional laser, an ablative fractional laser, and a full ablative laser on 40mg twice daily isotretinoin for four months. Clinical assessment and a 4-mm punch biopsy was performed at each treatment site during the six-month follow-up visit. While the sites treated with fractional laser showed normal appearing skin, the full ablative laser treatment site showed a mildly erythematous scar. However, researchers note the settings for this treatment site were "aggressive". Moradi et al 2005(Moradi *et al.*, 2005) treated 112 patients on isotretinoin for facial nevi, hair removal, acne scarring, and keloids with one of seven lasers. During a six-month follow-up, no significant changes on wound healing, long-standing erythema, scars, and keloid formation were observed. Gold et al 2020(Gold *et al.*, 2020) administered low-dose isotretinoin in combination with Nd:YAG laser treatments and found significant reduction in acne scarring without any complications.

Alissa et al 2011(Alissa, 2011) enrolled 100 patients on isotretinoin therapy for treatment with erbium, vascular, Q-switched alexandrite, 532 nm Q-switched, 1064 nm Nd:YAG, and non-ablative fractional laser. No hypertrophic scars or keloid development was noted. Mahadevappa et al 2016(Mahadevappa *et al.*, 2016) treated 163 patients with fractional or full face CO_2, fractional Er:YAG, Q switched Nd YAG, long pulse Nd-YAG, or long pulsed

diode lasers on concomitant isotretinoin for hair removal or acne scarring. Three patients exhibited transient erythema or pigmentation that resolved. Kwon et al(Kwon *et al.*, 2020) demonstrated statistically significant improvement from baseline of recalcitrant papulopustular rosacea with pulse dye laser, fractional microneedling, and concomitant isotretinoin without any adverse events.

Case Reports

Zachariae(Zachariae, 1988) observed one woman with rosacea undergo two argon laser sessions with minor transient erosions. One month after starting 60 mg daily isotretinoin, she was treated in the same area and found that the lesions took more than eight weeks to heal, and four weeks later she developed keloid scarring at these sites. A keloid on her left knee was found, indicating a tendency to form keloids. Bernestein and Geronemus(Bernestein and Geronemus, 1997) reported a case of an Asian woman treated for a capillary vascular malformation of her neck with a 585 nm pulsed dye laser. After five treatments without adverse effects, she began isotretinoin and developed keloid scarring two weeks after her next treatment.

Han et al(Han *et al.*, 2012) described a case of cutaneous Rosai-Dorfman Disease managed with 10 mg twice daily isotretinoin and pulsed dye laser treatment with no adverse events. Park et al(Park *et al.*, 2013) treated a 57-year-old woman with multiple eccrine hidrocystoma

with 20mg daily isotretinoin followed by a single CO_2 laser session. Good effect was achieved, though eventually the lesion recurred. Similarly, Noh et al(Noh *et al.*, 2014) used two sessions of CO_2 laser and isotretinoin 150mg/kg to clear previously laser-resistant sebaceous hyperplasia of the face, which responded well clinically without side effects or recurrence.

Pestoni et al(Pestoni Porvén, Vieira dos Santos and del Pozo Losada, 2017) used concomitant tretinoin and fractional CO_2 laser on two patients for successful treatment of nodulocystic acne, resulting in improvement without significant adverse events. In addition, Demirkan et al(Demirkan, 2019) used a single session of Er:YAG laser and isotretinoin to successfully treat multiple eccrine hidrocystoma without recurrence at one year. No adverse events were reported.

Ma et al(Ma *et al.*, 2020) successfully use six sessions of 595 nm pulse-dye laser treatment with isotretinoin to treat lupus miliaris disseminates faciei without side effects.

Expert Opinion

Patwardhan et al(Patwardhan *et al.*, 2012) reported that their practice has been treating patients on isotretinoin concomitantly with the alexandrite laser for hair reduction for over a decade. Due to early case reports, lower fluencies were used on patients, but have since been

modified to the same laser settings for both patients with and without a prescription for isotretinoin. The degree of erythema and perifollicular edema were comparable to those not on isotretinoin therapy. Patients are also treated with a Nd: YAG and microfractional erbium glass laser for acne scarring while on isotretinoin and the results have been comparable or superior to those patients not on oral isotretinoin.

Discussion

Summary

Studies considering concomitant laser and isotretinoin use consisted of 871 patients, the highest collated to date on this topic. Of these, 587 sought acne scar revision and 84 sought laser hair removal. Fourteen experienced adverse effects(Zachariae, 1988; Bernestein and Geronemus, 1997; Khatri, 2004, 2009; Cassano, Arpaia and Vena, 2005; Moradi *et al.*, 2009; Hann *et al.*, 2010; Chandrashekar *et al.*, 2014; Khatri, Iqbal and Bhawan, 2015); twelve of these were transient hyperpigmentation or eruptions resolving spontaneously. Three papers suggested that this was equal to the rate of complications in the control group (use of isotretinoin alone)(Moradi *et al.*, 2009; Chandrashekar *et al.*, 2014; Kim *et al.*, 2014). Two demonstrated keloid scarring. Both of these patients were cited in case reports that fall among the lowest level of evidence of all studies and among these two, one patient was

deemed "keloid-prone". This systematic review represents the largest cohort of patients assessed for adverse events to concomitant isotretinoin and laser therapy to date.

Quality Assessment

Recommendations on this important topic is limited by the lack of high-quality evidence of randomized controlled trials. Therefore, this systematic review does not include level 1 evidence. However, there are five level 2, ten level 3, three level 4, and only one level 5 report. The majority of studies included are level 3 or higher. This review considers a greater body of evidence than that used to formulate current guidelines.

It is important to consider the limitation of all studies included in this review, including pre-intervention (e.g. confounding, selection), peri-intervention (e.g. classification), and post-intervention (e.g. reporting) bias. Eight studies(Zachariae, 1988; Bernestein and Geronemus, 1997; Han *et al.*, 2012; Patwardhan *et al.*, 2012; Park *et al.*, 2013; Noh *et al.*, 2014; Pestoni Porvén, Vieira dos Santos and del Pozo Losada, 2017; Demirkan, 2019) were critically biased due to the inherent limitations of case reports and expert opinions of selective reporting and negative self-controls. The remainder were moderately biased, due to no pre-registered protocols, variable isotretinoin dosages and laser settings, and the subjective nature of outcome measures. Critically biased studies were the only to report keloid formation, whereas moderately biased studies reported transient adverse events, if any.

At a study level, limitations may include incomplete retrieval of all studies related to this topic or reporting bias. The inclusion of twelve databases and no language restrictions help counteract these forms of bias.

Adverse Events of Isotretinoin Alone

In considering any treatment regimen that includes more than one element, adverse events may be associated with both interventions together or due to one alone, crucial in the case of adverse events of concomitant isotretinoin and lasers. Spontaneous keloid transformation following isotretinoin therapy has been described in several case reports in which the patient has not been exposed to laser treatment, suggesting that these complications may be inherent to the medication rather than lasers.(Ginarte, Peteiro and Toribio, 1999; Dogan, 2006) Therefore, it is possible that the presentation of keloids in two patients included in this systematic review may be due to isotretinoin alone.

Recommendation

The summary of recommendations by treatment is described in Table 2. The majority of studies determine that laser intervention – whether for acne scar revision, hair removal, or otherwise – is associated with small or absent risk and produces a grade 1 recommendation

due to consistent findings. Contraindication produces a grade 2B recommendation low-quality evidence of two case reports of one patient each.

Adverse events associated with different lasers and dosages of isotretinoin are described in Table 3. Ablative, nonablative, or a combination of laser therapies may be used during systemic isotretinoin treatment. There are no reliable differences between ablative and non-ablative laser therapy as keloid formation occurred in patients under both modalities, and notably these were case reports from prior to the turn of the century in possibly patients that were keloid-prone at baseline. In addition, isotretinoin dosage does not appear to impact the occurrence of adverse events as a patient on 60mg qd developed a keloid, while no adverse events were noted in patients on even higher doses. Due to the two brief reports of adverse events occurring in patients prone to keloid formation, physicians should evaluate whether the patient is susceptible to pigmentation, scars, or keloid formation and consider a test treatment area prior to treatment as a standard (Zachariae, 1988; Bernestein and Geronemus, 1997). Patients should also be recommended to use a mild cleanser and moisturizer as well as sunscreen and sun avoidance post-treatment to decrease any possible associated risks (Alexiades-Armenakas, Dover and Arndt, 2008; Pozner and DiBernardo, 2016).

The results of this systematic review are promising for patients and providers wishing to continue isotretinoin during laser treatment. We conclude that though there may be a risk

associated with concomitant use of isotretinoin and lasers, the body of evidence indicates that this risk is relatively small or absent. Recent studies have demonstrated no difference in wound healing perioperatively between those individuals on systematic isotretinoin versus control(Tolkachjov *et al.*, 2017). Further robust studies should be conducted to provide additional evidence that may challenge the current guidelines contraindication.

Conclusion

The data presented fails to show long-term adverse effects of concomitant use of isotretinoin and lasers. It does not prove that isotretinoin use is safe at all dosages and with all lasers at all parameters. Further high-quality randomized controlled trials with a larger number of patients and treatments must be performed before it is concluded that concomitant use is completely safe in patients.

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Table 1. Results of Systematic Review on Concomitant Use of Lasers and Isotretinoin.

Author	Type of Study	Study Size	Patient Request	Laser	Frequency (t= treatment, s=session)	Dosage	Control	Follow-Up Period	Efficacy	Adverse Events	Level of Evidence
Zachariae 1988	CR	1	Rosacea	Argon, 1.3W,0.2 s	1t	60 mg QD	Self	4mo		Keloid formation in keloid-prone patient	4
Bernestein and Geronemus 1997	CR	1	Capillary Vascular Malformation	585nm pulse dye,6.0 J/cm^2	1t	Unknown	Self	0.5mo		Keloid formation	4
Khatri 2004	PUOLT	7	LHR	810nm diode, 80/90W, 300ms	$\bar{x}$ = 5t	20-80 mg QD		1mo	Satisfied hair removal	Transient bulla, resolved in 1 month	3
Cassano et al 2005	PUOLT	6	LHR	810nm diode	4-9s	0.3 - 0.5 mg/kg QD		Immediate	No cutaneous changes	Spontaneously healing sparse crusting	3

Moradi et al 2005	HUOLT	112	Facial Nevi (10),LHR (44),AS (53),Keloids (5)	quality-switched ruby,diode, intense pulsed,ER: YAG,Nlite,pulsed dye	Variable	Variable		6mo		None	3
Khatri and Garcia 2006	PUOLT	6	LHR	1200nm pulser, 22-27J/cm^2,20 ms	$\bar{x}$ = 4t	40-80 mg QD		6mo	Satisfied hair removal	None	3
Khatri 2009	PUOLT	11	LHR	1064nm Nd: YAG, 30-50 J/cm^2, 10-30 ms	$\bar{x}$ = 12t	0.5 mg/kg QD		Immediate	Rate of complications not increased when taking isotretinoin	Transient hyperpigmentation, resolved in 3 months	3
Moradi et al 2009	PCOLT	148	AS	(a) Nlite, 3 J/cm^2; (b) ER: YAG, 0.6-0.7 J/cm^2	(a) 3s and (b) 5 weekly s	1 mg/kg QD	Age-matched patients	6mo	Satisfied scar removal	Hyperpigmentation at equal rate (3%) in both groups.	2
Hann et al 2010	PUOLT	35	AS	1550 nm infrared fractional	$\bar{x}$ = 3t	10 mg QD		Immediate	80% patients moderate-excellent improvement	Transient mild acneiform eruption	3

Alissa et al 2011	PUOLT	100	Various	Erbium, vascular, Q-switched alexandrite, 532 nm Q-switched, 1064 nm Nd: YAG, and non-ablative fractional		Variable		Up to 7yrs	No hypertrophic scars or keloids		3
Leal and Cantu 2011	HCCT	60	AS	Fractionated erbium (50-70 mJ)	Variable	20 mg QD	Patients with acne scarring who had not taken isotretinoin during the study period		No difference in erythema, edema, and scabbing in recovery process between groups.		2
Patwardhan et al 2012	EO		LHR and AS	Long-pulsed Nd-YAG laser and microfractional erbium glass	Variable	Variable	Patients undergoing the same treatments not on isotretinoin.	Up to 10yrs	Erythema/perifollicular edema comparable. Acne scar resurfacing results better concomitant.		5

Han et al 2012	CR	1	Cutaneous Rosai-Dorfman Disease	pulsed dye		10 mg BID			Satisfactory clearance.		4
Jeong et al 2013	HUOLT	20	AS	Ablative fractional CO_2	1t	Variable		4yrs	Satisfactory clearance.		3
Park et al 2013	CR	1	Multiple eccrine hidrocystomas	Ultrapulse CO_2, 800W, 20-Hz, 0.3-msec	1t	20 mg 6w		1yr	Improvement but eventual recurrence		5
Noh et al 2014	CR	1	Sebaceous hyperplasia	CO_2	2t	150 mg/kg		2yrs	Clearance		5
Yoon et al 2014	PCOLT	35	AS	1550 nm erbium-doped, 35-40 mJ, 8 passes	3-4 weeks for 2-6s	10 mg QD	Patients with acne scarring who had not taken isotretinoin for at least six months	Immediate Assessment After Last Session	94% concomitant showed improvement versus 88% controls		2

Chandrashekar et al 2014	HCCT	60	AS (50) and LHR (10)	(a) CO_2; (b) diode 980 nm hair removal	4t every 6 weeks	0.5 mg/kg QD + topical medication	topical medication only	6mo	(a) Excellent scar revision; (b) Safe hair removal	(a) 8% patients transient hyperpigmentation, resolved 1-2 months; (b) none	2
Kim et al 2014	HCCT	20	AS	CO_2, 30 W, 1 ms	1-6s	10-40 mg/d QD	Patients who had not taken isotretinoin	48mo	Scar improvement	Erythema/ crust, resolved one month.	2
Khatri et al 2015	PUOLT	1	AS	(a) Nonablative fractional (1540 nm, 100 mJ/mB, 3 passes); (b) ablative fractional laser (erbium:YAG 2940 nm, 91 J/cm^2, 3 passes); (c) full ablative (erbium:YAG 2940 nm, 2 J, 8 passes)	1t	40 mg BID		6mo		(a) None; (b) None; (c) Mild erythematous scar	3

Mahadevappa et al, 2016	PC	71	Hair Reduction or AS	(a) Long-pulsed Nd:YAG (1064nm,9mm,30ms,40 J/cm^2) (b) Fractional ER:YAG 2940nm, long pulse or scanner (c) Fractional CO_2 30 mj,pulse 0.04s,100 pixel (d) Full face conventional CO_2 resurfacing 3mm spot,500Hz (e) Q-switched Nd:YAG 1.5mm spot,400mj	Varies	2-110 mg/kg	None	Varies	Not reported	(a) None (b) resolving post-inflammatory pigmentation (c-d) None (e) transient erythema	2

Saluja et al 2017	RSFCT	10	AS	Erbium doped 1550nm NAFL	3t 4 weeks apart	125-325 mg/kg	Split-face	4mo	50% moderate imporvement, 10% significant improvement		2
Pestoni et al 2017	CS	2	Nodulocystic Acne	10600nm CO_2 fractional 38-42 mJ,5.51J/cm^2	1t	0.05%	None	2-10mo	Significant improvement.	Transient hyperpigmentation, self-resolving	5
Xia et al 2018	RSFCT	18	Acne	1550 nm Erbium:glass fractional (20 mJ/cm^2, 100-169 points per area)	Three treatments	10 mg QD	Split-face	Immediate	Comedo lesoons significant improved in NAFL-treated half face.	Mild transient erythema	2
Demirkan et al 2019	CR	1	Multiple eccrine hidrocystoma	Er:YAG (19J, 2mm spot size, 3Hz)	Single session	20 mg QD	None	1yr	Successful treatment of lesions without recurrence.		1
Gold et al 2020	PC	46	AAS	Nd:YAG	Twelve treatments, two week intervals	0.2-0.3 mg/kg/d	None	Immediate	Baseline improvement.		2

Kwon et al 2020	RUOLT	25	Recalcitrant Rosacea	595nm Pulsed-dye (5-8 J/cm^2)	3t	10 mg QD	None	4mo	Baseline improvement.		3
Kim et al 2020	ROS	71	AAS	Ablative fractional	Varies	Varies	Patients not on isotretinoin.	Varies	Scar decrease more pronounced on concomitant therapy.		3
Ma et al 2020	CR	1	Lupus miliaris disseminatus faciei	595 nm pulsed dye 7.5-8.5 J/cm^2, 1.5ms	6s	10 mg QD	None	5mo	Effective treatment without recurrence.		1

Type of Study
CR:Case Report
CS: Case Series
EO: Expert Opinion
HCCT: Historical Controlled Clinical Trial
PC: Prospective Cohort
PCOLT: Prospective Controlled Open-Labeled Trial
PUOLT: Prospective Uncontrolled open-labeled trial
ROS: Retrospective Observational Study
RSFCT: Randomized Split-Face Controlled Trial
RUOLT: Retrospective uncontrolled open-labeled trial

Patient Request
AAS: Acne and Acne Scarring | AS: Acne Scarring
LHR: Laser Hair Removal

Table 2. Summary of Recommendations by Laser Intervention

Recommendation		**Grade of Recommendation**(Robinson *et al.*, 2008)	**Level of Evidence**(Howick *et al.*, 2011)
Safe	Acne or Acne Scar Revision(Moradi *et al.*, 2009, 2005; Hann *et al.*, 2010; Leal and Cantu, 2011; Patwardhan *et al.*, 2012; Jeong *et al.*, 2013; Chandrashekar *et al.*, 2014; Yoon *et al.*, 2014; Kim *et al.*, 2014, 2020; Khatri, Iqbal and Bhawan, 2015; Mahadevappa *et al.*, 2016; Pestoni Porvén, Vieira dos Santos and del Pozo Losada, 2017; Saluja *et al.*, 2017; Xia *et al.*, 2018; Gold *et al.*, 2020)	1	2, 3, and 5
	Laser Hair Removal(Khatri, 2004, 2009;	1	2, 3, and 5
		1	3, 4, and 5

	Cassano, Arpaia and Vena, 2005; Moradi *et al.*, 2005; Khatri and Garcia, 2006; Patwardhan *et al.*, 2012; Chandrashekar *et al.*, 2014; Mahadevappa *et al.*, 2016)		
	Other(Moradi *et al.*, 2005; Alissa, 2011; Han *et al.*, 2012; Park *et al.*, 2013; Noh *et al.*, 2014; Demirkan, 2019; Kwon *et al.*, 2020; Ma *et al.*, 2020)		
Contraindicated	Acne Scar Revision Laser Hair Removal Other(Zachariae, 1988; Bernestein and Geronemus, 1997)	2B	4

Table 3. Adverse Events Sorted by Laser Subtype and Isotretinoin Dose

Ablative/ Nonablative	Laser Type	Laser	Dosage	Adverse Events	Author
Ablative	Argon	Argon, 1.3W,0.2 s	60 mg QD	Keloid formation in keloid-prone patient	Zachariae 1988
	CO2	10600nm CO_2 fractional 38-42 mJ,5.51J/cm^2	0.0005	Transient hyperpigmentation, self-resolving	Pestoni et al 2017
		1550 nm infrared fractional	10 mg QD	Transient mild acneiform eruption	Hann et al 2010
		CO_2, 30 W, 1 ms	10-40 mg/d QD	Erythema/ crust, resolved one month.	Kim et al 2014
		Ultrapulse CO_2, 800W, 20-Hz, 0.3-msec	20 mg 6w		Park et al 2013

		CO_2	150 mg/kg		Noh et al 2014
		Ablative fractional CO_2	Variable		Jeong et al 2013
		Ablative fractional	Varies		Kim et al 2020
	Erbium	1550 nm erbium-doped, 35-40 mJ, 8 passes	10 mg QD		Yoon et al 2014
		Er:YAG (19J, 2mm spot size, 3Hz)	20 mg QD		Demirkan et al 2019
		Fractionated erbium (50-70 mJ)	20 mg QD		Leal and Cantu 2011
		Erbium doped 1550nm NAFL	125-325 mg/kg		Saluja et al 2017
Nonablative	Diode	810nm diode	0.3 - 0.5 mg/kg QD	Spontaneously healing sparse crusting	Cassano et al 2005
		810nm diode, 80/90W, 300ms	20-80 mg QD	Transient bulla, resolved in 1 month	Khatri 2004
	Erbium: glass fractional	1550 nm Erbium:glass fractional (20 mJ/cm^2, 100-169 points per area)	10 mg QD	Mild transient erythema	Xia et al 2018
	Multiple	Long-pulsed Nd-YAG laser and microfractional erbium glass	Variable		Patwardhan et al 2012
	Nd:YAG	Nd:YAG	0.2-0.3 mg/kg/d		Gold et al 2020
		1064nm Nd: YAG, 30-50 J/cm2, 10-30 ms	0.5 mg/kg QD	Transient hyperpigmentation, resolved in 3 months	Khatri 2009
	Pulsed Dye	pulsed dye	10 mg BID		Han et al 2012

		595nm Pulsed-dye (5-8 J/cm^2)	10 mg QD		Kwon et al 2020
		595 nm pulsed dye 7.5-8.5 J/cm^2, 1.5ms	10 mg QD		Ma et al 2020
		585nm pulse dye,6.0 J/cm^2	Unknown	Keloid formation	Bernestein and Geronemus 1997
	Pulser	1200nm pulser, 22-27J/cm2,20 ms	40-80 mg QD	None	Khatri and Garcia 2006
Multiple	Multiple	(a) CO_2; (b) diode 980 nm hair removal	0.5 mg/kg QD + topical medication	(a) 8% patients transient hyperpigmentation, resolved 1-2 months; (b) none	Chandrashekar et al 2014
		(a) Nlite, 3 J/cm^2; (b) ER: YAG, 0.6-0.7 J/cm^2	1 mg/kg QD	Hyperpigmentation at equal rate (3%) in both groups.	Moradi et al 2009
		(a) Long-pulsed Nd:YAG (1064nm,9mm,30ms,40 J/cm^2) (b) Fractional ER:YAG 2940nm, long pulse or scanner (c) Fractional CO2 30 mj,pulse 0.04s,100 pixel (d) Full face conventional CO2 resurfacing 3mm spot,500Hz (e) Q-switched Nd:YAG 1.5mm spot,400mj	2-110 mg/kg	(a) None (b) resolving post-inflammatory pigmentation (c-d) None (e) transient erythema	Mahadevappa et al, 2016
		(a) Nonablative fractional (1540 nm, 100 mJ/mB, 3 passes); (b) ablative fractional laser (erbium:YAG 2940 nm, 91 J/cm^2, 3 passes); (c) full ablative (erbium:YAG 2940 nm, 2 J, 8 passes)	40 mg BID	(a) None; (b) None; (c) Mild erythematous scar	Khatri et al 2015
		quality-switched ruby,diode, intense pulsed,ER: YAG,Nlite,pulsed dye	Variable	None	Moradi et al 2005

		Erbium, vascular, Q-switched alexandrite, 532 nm Q-switched, 1064 nm Nd: YAG, and non-ablative fractional	Variable		Alissa et al 2011

Figure Legend

Supplemental Figure 1 – PRISMA Flowchart for Search Strategy – This figure shows the number of records in the identification, eligibility, screening, and inclusion stages of the databases' searches.

Supplemental Tables

Sup Table 1. Inclusion & Exclusion Criteria.

Inclusion	Exclusion
• Conducted in humans • Includes one or more of the key search terms identified • Quantitative or qualitative studies or reviews • From inception to February 1st, 2017 • Available	• Commentaries or policy documents • Non-skin treatment sites (e.g. eye) • Studies where patients were instructed to discontinue isotretinoin use • Duplicate data or withdrawn studies

Sup Table 2. Risk of Bias Assessment Using Risk of Bias in Non-Randomized Studies – of Interventions (ROBINS-I) Tool.

Author	Confounding	Selection	Classification	Deviations	Missing Data	Measurement	Reporting	Overall
Zachariae 1988	Critical	Critical	Moderate	Low	Low	Serious	Critical	Critical
Bernestein and Geronemus 1997	Critical	Critical	Moderate	Low	Low	Serious	Critical	Critical
Khatri 2004	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate
Cassano et al 2005	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate
Moradi et al 2005	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Khatri and Garcia 2006	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Khatri 2009	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Moradi et al 2009	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate
Hann et al 2010	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Alissa et al 2011	Moderate	Low	Low	Low	No Information	Moderate	Moderate	Moderate
Leal and Cantu 2011	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Patwardhan et al 2012	Critical	Critical	Critical	Critical	Critical	Critical	Critical	Critical
Han et al 2012	Critical	Critical	Moderate	Low	Low	No Information	Critical	Critical
Park et al 2013	Critical	Critical	Moderate	Low	Low	No Information	Critical	Critical
Noh et al 2013	Critical	Critical	Moderate	Low	Low	No Information	Critical	Critical
Jeong et al 2013	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Yoon et al 2014	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Chandrashekar et al 2014	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Kim et al 2014	Moderate	Moderate	Low	Low	Low	Low	Moderate	Moderate
Khatri et al 2015	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Mahadevappa et al 2016	Moderate	Low	Low	Low	No Information	Moderate	Moderate	Moderate
Saluja et al 2017	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Pestoni et al 2018	Critical	Critical	Moderate	Low	Low	No Information	Critical	Critical
Xia et al 2018	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Demirkan et al 2019	Critical	Critical	Moderate	Low	Low	No Information	Critical	Critical
Gold et al 2020	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Kwon et al 2020	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Kim et al 2020	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Ma et al 2020	Critical	Critical	Moderate	Low	Low	No Information	Critical	Critical

Scale (in ascending order)

No Information | Low | Moderate | Serious | Critical

Supplemental Figures

- Figure 1 – The number of records in the identification, eligibility, screening, and inclusion stages of the databases' searches are represented in this PRISMA Flowchart for Search Strategy.

Supplemental Figure 1.