

# Isotretinoin and Timing of Procedural Interventions

## A Systematic Review With Consensus Recommendations

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**IMPORTANCE** The notion that systemic isotretinoin taken within 6 to 12 months of cutaneous surgery contributes to abnormal scarring or delayed wound healing is widely taught and practiced; however, it is based on 3 small case series from the mid-1980s.

**OBJECTIVE** To evaluate the body of literature to provide evidence-based recommendations regarding the safety of procedural interventions performed either concurrently with, or immediately following the cessation of systemic isotretinoin therapy.

**EVIDENCE REVIEW** A panel of national experts in pediatric dermatology, procedural/cosmetic dermatology, plastic surgery, scars, wound healing, acne, and isotretinoin was convened. A systematic PubMed review of English-language articles published from 1982 to 2017 was performed using the following search terms: isotretinoin, 13-cis-retinoic acid, Accutane, retinoids, acitretin, surgery, surgical, laser, ablative laser, nonablative laser, laser hair removal, chemical peel, dermabrasion, wound healing, safety, scarring, hypertrophic scar, and keloid. Evidence was graded, and expert consensus was obtained.

**FINDINGS** Thirty-two relevant publications reported 1485 procedures. There was insufficient evidence to support delaying manual dermabrasion, superficial chemical peels, cutaneous surgery, laser hair removal, and fractional ablative and nonablative laser procedures for patients currently receiving or having recently completed isotretinoin therapy. Based on the available literature, mechanical dermabrasion and fully ablative laser are not recommended in the setting of systemic isotretinoin treatment.

**CONCLUSIONS AND RELEVANCE** Physicians and patients may have an evidence-based discussion regarding the known risk of cutaneous surgical procedures in the setting of systemic isotretinoin therapy. For some patients and some conditions, an informed decision may lead to earlier and potentially more effective interventions.

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The notion that isotretinoin (13-cis-retinoic acid) use causes abnormal scarring or delayed wound healing is widely taught.<sup>1-3</sup> This concept stems from 3 case series published in the mid-1980s describing a total of 11 patients with delayed healing and keloid development following mechanical dermabrasion (10 patients) and argon laser treatment (1 patient).<sup>4-6</sup> The extrapolated recommendation that it was “probably wise” to postpone all “surgical procedures in retinoid treated patients until after discontinuation of therapy and until the activity of the retinoids has had time to subside”<sup>6(p705)</sup> has persisted despite increasing reports to the contrary.

The goals of this consensus panel were as follows: (1) establish the level of evidence for delaying procedural interventions in the setting of concurrent or recent systemic isotretinoin; (2) where possible, make evidence-based recommendations for delaying or not delaying therapeutic interventions in this specific setting; (3) create a comprehensive source of evidence that permits physicians from multiple specialties and their patients to reach an informed decision about unknown or underlying risk. This report also highlights the need for additional well-controlled, prospective studies that better elucidate the effect of isotretinoin use on scarring and wound healing.

## Methods

A PubMed review of published data from 1982 to 2017 was performed using the following search terms: isotretinoin, 13-cis-retinoic acid, Accutane, retinoids, acitretin, surgery, surgical, laser, ablative laser, nonablative laser, laser hair removal, chemical peel, dermabrasion, wound healing, safety, scarring, hypertrophic scar, and keloid. The search was limited to publications in the English language. Five major topics were identified: dermabrasion, chemical peel, cutaneous surgery, laser hair removal, and ablative/nonablative laser. The literature was assessed using the Oxford Centre for Evidence-Based Medicine's Levels of Evidence and Grades of Recommendation.<sup>7</sup>

A panel of national experts in pediatric dermatology, procedural/cosmetic dermatology, plastic surgery, scars, wound healing, acne, and isotretinoin was convened at the 74th Annual Meeting of the American Academy of Dermatology in March 2016. Each topic was assigned to a team of at least 2 reviewers (including a pediatric dermatologist and a procedural dermatologist), and each topic was independently reviewed by at least 2 different teams. Each team presented their findings to the group for discussion. Evidence-based recommendations were proposed and group consensus was obtained. Over the next year, the recommendations were further critiqued by respected wound healing and scar experts, plastic surgeons, pediatric dermatologists, and procedural dermatologists (including 1 of the authors of the original dermabrasion studies from which the recommendation to avoid procedural interventions originated).

## Results

Thirty-two clinically oriented publications in English provided details of 1485 procedures in the setting of systemic isotretinoin treat-

### Key Points

**Question** What is the evidence behind the medical dictum prohibiting procedural interventions in the setting of isotretinoin therapy?

**Findings** This systematic review found insufficient evidence to support delaying manual dermabrasion, superficial chemical peels, cutaneous surgery, laser hair removal, and fractional ablative and nonablative laser procedures for patients who are currently taking or have recently completed isotretinoin therapy. Mechanical dermabrasion and fully ablative laser procedures are currently not recommended.

**Meaning** Previously prohibited procedures may be offered to a patient when accompanied by an evidence-based discussion of the risks and benefits of a procedure as part of gaining informed consent.

ment in case series, case reports, cohort studies, systematic reviews, and randomized clinical trials, which were critiqued by our panel in the 5 major topic areas.

### Dermabrasion

The concern about mechanical dermabrasion (using a diamond fraise or a wire brush/diamond fraise attached to a motorized handle) in the setting of isotretinoin use arose from a series of case reports from 1985 to 1994. Roenigk et al<sup>4</sup> published the first article suggesting an association of isotretinoin use with possible wound healing complications in patients undergoing full-face mechanical dermabrasion. Nine patients treated concomitantly with, or having recently completed, isotretinoin therapy healed at a normal rate with no post-operative complications. An addendum to the article stated that 2 additional patients developed keloids following mechanical dermabrasion after recent therapy with isotretinoin.<sup>4</sup> Two case series published in 1986 and 1988 reported a total of 8 patients concomitantly receiving, or having completed isotretinoin treatment 2 to 6 months prior, with delayed healing and keloid development following mechanical dermabrasion.<sup>5,6</sup> A single case report published in 1994 noted delayed-onset hypertrophic scarring of the cheeks when mechanical dermabrasion was followed with a course of isotretinoin therapy.<sup>8</sup>

Manual dermabrasion (a minimal to medium-depth resurfacing modality performed without connection to a rotation engine) in the setting of systemic isotretinoin treatment was first investigated by Bagatin et al<sup>9</sup> in 2010. Seven patients, who were taking isotretinoin, underwent a 1-cm<sup>2</sup> test spot with manual dermabrasion using a diamond fraise. The patients were followed serially for 180 days, and all patients (including 1 with a previous history of hypertrophic acne scars) healed without complications.<sup>9</sup> Partial to full-face chemabrasion using trichloroacetic acid (TCA), 35%, followed by manual sandpaper dermabrasion, which was performed until the appearance of a “bloody dew,” was performed on 10 patients in 2012 with depressed facial scars (Fitzpatrick skin types II-V) who had completed isotretinoin therapy 1 to 3 months prior. All patients, even those with previous hypertrophic acne scars, had normal healing observed at 6-month follow-up.<sup>10</sup>

In 2016, a multicenter, 1-year, prospective interventional study of microdermabrasion evaluated 504 procedural interventions performed on 183 patients with Fitzpatrick skin types IV and V, 66% of

Table 1. Summary of Evidence of Dermatologic Procedures in the Setting of Isotretinoin Use

| Source                                    | Trial Design              | Patients, No. | Quality of Evidence | Isotretinoin Use                           | Isotretinoin Dose       | Type of Procedure   | Outcome   |
|---|---------------------------|---------------|---------------------|--|-------------------------|---|---|
| Roenigk et al, <sup>4</sup> 1985          | Case series               | 11            | 4                   | Concomitant (5 patients), or 2-11 mo prior | 0.5-1 mg/kg             | Mechanical dermabrasion: all patients: full face (diamond or diamond fraise/wire brush)   | Normal healing in all 9 originally reported patients, keloid development in 2 additional patients (isotretinoin dose unspecified) |
| Rubenstein et al, <sup>5</sup> 1986       | Case series               | 6             | 4                   | Concomitant (3 patients), or 2-6 mo prior  | 0.5-1 mg/kg             | Mechanical dermabrasion: 5 patients: full face (diamond or diamond fraise/wire brush); 1 patient: cheeks and temples (diamond fraise) | Development of keloids  |
| Zachariae, <sup>6</sup> 1988              | Case series               | 2             | 4                   | Concomitant                                | 60 mg                   | Mechanical dermabrasion: left cheek (1); nose (1)   | Development of keloids  |
| Katz and MacFarlane, <sup>8</sup> 1994    | Case report               | 1             | 5                   | 8 wk after                                 | Unspecified             | Mechanical dermabrasion: full face (extra-coarse diamond fraise)  | Hypertrophic scarring   |
| Bagatin et al, <sup>9</sup> 2010          | Case series               | 7             | 4                   | Concomitant                                | 10-40 mg                | Manual dermabrasion: all patients: 1-cm <sup>2</sup> area of depressed facial scars (cheek, forehead, nose, temporal area)            | Normal healing (180 d follow-up)  |
| Picose et al, <sup>10</sup> 2012          | Prospective cohort        | 10            | 2                   | 1-3 mo prior                               | 122-161 mg/kg           | Manual dermabrasion: manual (sandpaper) preceded by TCA, 35%  | Normal healing  |
| Mahadevappa et al, <sup>11</sup> 2016     | Prospective cohort        | 18            | 2                   | Concomitant or prior to                    | 10-40 mg                | Microdermabrasion: microdermabrasion (aluminum), 44 sessions  | Normal healing  |
| Hernandez-Perez et al, <sup>12</sup> 2000 | Randomized clinical trial | 120           | 1                   | Concomitant                                | 10-20 mg 3 times weekly | Chemical peels: resorcinol  | Normal healing (45 peels)   |
| Picose et al, <sup>10</sup> 2012          | Prospective cohort        | 10            | 2                   | 1-3 mo prior                               | 122-161 mg/kg           | Chemical peels: TCA 35%   | Normal healing (10 peels), followed up for 180 d  |
| Kar et al, <sup>13</sup> 2013             | Prospective cohort        | 60            | 2                   | Concomitant                                | 20 mg                   | Chemical peels: SA, 20%, every 2 weeks for 16 weeks   | Normal healing (240 peels), followed up for 16 weeks  |
| Gerber et al, <sup>14</sup> 2014          | Case report               | 1             | 5                   | 3 wk prior                                 | 10 mg 3 times weekly    | Chemical peels: GA, 70%   | Erythema, erosions, PIH ("repetitive treatments" for several months)  |
| Mahadevappa et al, <sup>11</sup> 2016     | Prospective cohort        | 80            | 2                   | Concomitant or prior to                    | 10-40 mg                | Chemical peels: GA (147 peels), salicylic acid (30 peels), TCA (4 peels), combination (65 peels)                                      | Normal healing (237 peels), keloid (1 incidence, GA peel), transient erythema (8 incidences, GA and combination peels)            |

Abbreviations: GA, glycolic acid; PIH, postinflammatory hyperpigmentation; TCA, trichloroacetic acid.

whom were concomitantly taking isotretinoin, the remainder having recently completed therapy. In this study, microdermabrasion (epidermal ablation without extension into the dermis using a handheld device that streams tiny crystals across the skin) was performed 44 times without adverse effects<sup>11</sup> (Table 1).

#### Consensus Recommendation

On the basis of existing literature, abnormal scarring may be associated with mechanical dermabrasion in the setting of recent isotretinoin use and is not recommended. In contrast to mechanical dermabrasion, there is insufficient evidence to delay manual or microdermabrasion for patients who are concurrently receiving or have recently completed isotretinoin therapy. Additional prospective, well-controlled clinical trials are recommended (Table 2).

#### Chemical Peel

Many trials have reported favorable outcomes for patients taking systemic isotretinoin while undergoing a chemical peel. Two cohort trials describing chemabrasion using TCA, 35% (10 patients, discussed in the Dermabrasion subsection), and serial salicylic acid, 20%, peels (30 patients, treated every 2 weeks for 16 weeks while taking isotretinoin) reported favorable cosmetic outcomes in the setting of isotreti-

noin use, without adverse effects on healing.<sup>10,13</sup> Forty-five resorcinol peels performed on 20 patients concomitantly treated with low-dose isotretinoin demonstrated statistically significant cosmetic improvement of aging compared with patients not taking isotretinoin.<sup>12</sup>

There are a few reports of unfavorable outcomes. Persistent hyperpigmentation, erosions, and scarring following a glycolic acid, 70%, peel was reported in a patient who had discontinued her unmonitored, unregulated course of isotretinoin use 3 weeks prior to treatment.<sup>14</sup> Mahadevappa et al<sup>11</sup> performed 246 chemical peels in the setting of concomitant or recent isotretinoin therapy: 147 glycolic acid peels, 65 combination peels, 30 salicylic acid peels, and 4 TCA peels. One patient developed keloids on the face and the untreated chest following a glycolic acid peel. The only other sequela noted was transient erythema following 6 glycolic acid peels and 2 combination peels (Table 1).

#### Consensus Recommendation

There is reasonable evidence to suggest that superficial chemical peels in the setting of low-dose isotretinoin treatment may not be associated with increased scarring or poor wound healing (contrary to previous extrapolations). Additional prospective, well-

controlled clinical trials investigating all depths of peels in the setting of a wide dose range of isotretinoin treatment are recommended (Table 2).

### Cutaneous Surgery

Patients treated with a variety of cutaneous surgical procedures while receiving systemic isotretinoin have been reported to heal without sequelae: 12 blepharoplasties, 9 liposuctions, 9 fat transfers, 9 face-lifts, 8 skin biopsies, 7 subcisions, 2 excisions, and 2 punch elevations of scars.<sup>11,12</sup> A 2016 systematic review of oral isotretinoin use and surgical procedures concluded that the current data on coagulation disorders, liver toxic effects, kidney toxic effects, arrhythmia, and infection associated with isotretinoin use indicate that it is safe to operate on patients taking isotretinoin (as long as they are healthy and preoperative blood test results fall within normal limits).<sup>15</sup> Regarding the specific setting of major reconstructive surgery requiring the mobilization of muscle flaps, patients taking isotretinoin and presenting with creatine phosphokinase (CPK) levels higher than 2-fold of normal may "present an unusual risk factor for muscle flap failure: rhabdomyolysis." Consequently, the authors suggested that, "if possible, surgery should wait until the patient displays normal CPK levels or, at least, CPK levels below twofold of normal."<sup>15(p146)</sup> However, no references for this specific recommendation were provided in the report, and a thorough review failed to reveal literature specifically addressing this warning. In addition, a nonblinded, observational cohort study of patients taking acitretin (a second-generation retinoid with a mechanism of action similar to that of isotretinoin) contributes to the body of surgical evidence. Twenty-nine organ transplant recipients underwent Mohs micrographic or excisional surgery for skin cancer. Eleven patients with a total of 41 wounds were concomitantly treated with acitretin, and 18 patients with a total of 44 wounds were not taking systemic retinoids. The wounds were reconstructed via layered linear closure, full-thickness skin graft, or flap or allowed to heal by secondary intention. No statistically significant differences between the 2 groups were found regarding incidences of infection, dehiscence, hypertrophic granulation tissue, or hypertrophic scarring.<sup>16</sup> It should be noted, however, that immunosuppressed transplant recipients are typically an older cohort compared with the adolescent acne population and may be less likely to develop hypertrophic scars. Low-quality safety evidence was contributed by case reports (Table 3).<sup>17,19-22</sup>

Sharma et al<sup>18</sup> reported a higher rate of postoperative alveolar osteitis among 26 patients who underwent wisdom tooth extraction while concomitantly taking isotretinoin or who had completed treatment 1 month prior to the procedure; however, a direct association with isotretinoin use could not be confirmed due to small sample size. All patients healed without further complications.<sup>18</sup>

### Consensus Recommendation

There is insufficient evidence to delay cutaneous surgery for patients currently taking or having recently completed isotretinoin therapy. Testing preoperative CPK level is not warranted, particularly for cutaneous surgery not involving a muscle flap or pedicle, because elevated creatine kinase level is a common and most often benign phenomenon in patients taking isotretinoin.<sup>23</sup> Additional prospective, well-controlled clinical trials are recommended. This includes a rigorous evaluation of the aforementioned specific warn-

Table 2. Summary of Panel Recommendations

| Procedural Intervention                   | Consistency of Evidence | Recommendation  | Strength of Recommendation |
|---|-------------------------|---|----------------------------|
| Mechanical dermabrasion                   | Inconsistent            | Not recommended   | D                          |
| Manual dermabrasion and microdermabrasion | Consistent              | There is insufficient evidence to delay manual or microdermabrasion   | B                          |
| Chemical peel                             | Consistent              | There is insufficient evidence to delay superficial chemical peels  | B                          |
| Cutaneous surgery                         | Inconsistent            | There is insufficient evidence to delay cutaneous surgery   | D                          |
| Laser hair removal                        | Consistent              | There is insufficient evidence to delay laser hair removal  | B                          |
| Fractional ablative/nonablative laser     | Consistent              | There is insufficient evidence to delay fractional ablative or nonablative laser procedures. Fully ablative laser procedures are not recommended at this time | B                          |

ing that muscle flap insertion should be delayed until the patient displays normal CPK levels or, at least, CPK levels below 2-fold of normal (Table 2).

### Laser

Laser interventions represent the most studied procedural category in patients taking isotretinoin. Although scarcely mentioned in the literature in the 1980s and 1990s (1 patient with "keloidal tendencies" was reported to have developed keloids following argon laser therapy, as did 1 patient after pulsed dye laser therapy),<sup>6,24</sup> in the past 2 decades hundreds of patients have been reported to have healed normally following treatment with lasers for the following indications: hair removal, acne scarring, and removal of superficial benign cutaneous lesions.

### Laser Hair Removal

Four case series reported normal healing of a total of 30 patients concomitantly taking isotretinoin treated with diode, long-pulse flash lamp, and neodymium-doped yttrium aluminum garnet (Nd:YAG) lasers.<sup>25-28</sup> In a 2012 research letter, Patwardhan et al<sup>29</sup> reported more than 10 years of experience treating patients who were taking isotretinoin with the alexandrite laser with "no untoward side effects." Exact numbers of patients, isotretinoin doses, or settings were not detailed in the letter.<sup>29</sup> Ten patients (5 concomitantly taking isotretinoin) underwent hair removal via Nd:YAG and diode laser, and intense pulsed light in a comparative, retrospective cohort study published in 2014. All healed normally.<sup>30</sup> In the 1-year interventional prospective study published by Mahadevappa et al<sup>11</sup> in 2016, no adverse effects were noted following 13 treatments with the long-pulsed diode laser, 4 with the long-pulsed Nd:YAG laser, and 9 with intense pulsed light (Table 4).

### Consensus Recommendation

There is insufficient evidence to delay laser and light-based hair removal for patients who are currently taking or have recently com-

Table 3. Summary of Evidence of Surgery in the Setting of Isotretinoin Use

| Source                                    | Trial Design                   | Patients, No. | Quality of Evidence | Isotretinoin Use                              | Isotretinoin Dose                     | Type of Surgery  | Outcome   |
|---|--------------------------------|---------------|---------------------|---|---------------------------------------|--|---|
| Hernandez-Perez et al, <sup>12</sup> 2000 | Randomized clinical trial      | 120           | 1                   | Concomitant                                   | 10-20 mg 3 times weekly (60 patients) | Blepharoplasty (12), liposuction (9), fat transfer (9), facelift (9)   | Normal healing  |
| Tan and Tope, <sup>16</sup> 2004          | Prospective cohort             | 29            | 2                   | Concomitant                                   | Acitretin, 10-50 mg (11 patients)     | NMSC excision; acitretin: 33 reconstructions, 8 secondary intention; control: 33 reconstructions, 11 secondary intention | No statistically significant differences between groups: infection, dehiscence, hypertrophic granulation tissue, or hypertrophic scarring |
| Allen and Rhee, <sup>17</sup> 2005        | Case series                    | 3             | 4                   | 7 mo, 1 y, and 2 y after                      | Unspecified                           | Rhinoplasty  | Skin thinning, nasal tip deformity  |
| Sharma et al, <sup>18</sup> 2012          | Retrospective cohort           | 26            | 3                   | Concomitant, or within 1 mo prior             | Unspecified                           | Wisdom tooth extraction  | Higher rate of alveolar osteitis (11% vs average cited rate of 3%-5%), otherwise normal healing   |
| Larson et al, <sup>19</sup> 2012          | Case report                    | 1             | 5                   | 4 mo prior                                    | Unspecified                           | Wide excision of hidradenitis suppurativa  | Normal healing of secondary intention wounds (axilla, scalp, genitalia, gluteal folds)  |
| Huoh and Chang, <sup>20</sup> 2013        | Case report                    | 1             | 5                   | Concomitant                                   | Unspecified                           | Incision and drainage of MRSA lip abscess  | Normal healing  |
| Yew and Pan, <sup>21</sup> 2014           | Case report                    | 1             | 5                   | Immediately following                         | 20 mg, tapered over 8 mo              | Surgical debulking of genital warts  | Normal healing  |
| Wootton et al, <sup>22</sup> 2014         | Systematic review, case report | 1             | 1                   | Prior to, and immediately following treatment | 20-80 mg                              | Shoulder arthroscopy   | Normal healing  |
| Ungarelli et al, <sup>15</sup> 2016       | Systematic review              | NA            | 1                   | NA  | NA                                    | NA   | Skeletal muscle flaps may be compromised  |
| Mahadevappa et al, <sup>11</sup> 2016     | Prospective cohort             | 20            | 2                   | Concomitant or prior to                       | 10-40 mg                              | Excision (2), subcision (7), biopsy (8), punch elevation (2), dental extraction (1)                                      | Normal healing  |

Abbreviations: NMSC, nonmelanoma skin cancer; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not applicable.

pleted isotretinoin therapy. Additional prospective, well-controlled clinical trials are recommended (Table 2).

### Ablative/Nonablative Fractional Laser

There are many case series and 1 randomized clinical trial demonstrating normal wound healing after treatment with ablative and nonablative fractional lasers in patients receiving systemic isotretinoin. In 2011, Leal and Cantu<sup>31</sup> reported 60 patients treated with a 1550-nm nonablative fractionated erbium laser for acne scarring: 30 patients concomitantly taking isotretinoin and 30 patients who had completed a course of isotretinoin treatment more than 6 months prior. There was no difference in either the recovery process or the final cosmetic improvement between the 2 groups.<sup>31</sup> Three case reports of successful, uncomplicated treatment with a 10 600-nm carbon dioxide (CO<sub>2</sub>) laser were published between 2012 and 2014: facial resurfacing with an ablative fractionated CO<sub>2</sub> laser following a 6-month course of isotretinoin, CO<sub>2</sub> laser ablation of multiple eccrine hidrocystomas performed immediately following a 6-week course of isotretinoin treatment, and clearance of sebaceous hyperplasia with 3 CO<sub>2</sub> laser treatments (type unspecified) followed immediately by isotretinoin treatment.<sup>32,33,36</sup> Twenty patients (Fitzpatrick skin types III and IV; 18 concomitantly taking isotretinoin, 2 who had completed treatment 4 weeks prior) underwent 1 to 6 full-face fractional ablative CO<sub>2</sub> laser resurfacing treatments. All patients healed with normal postprocedural reepithelialization and no evidence of scarring at 6-month follow-up.<sup>35</sup> A randomized clinical trial of 35 patients taking low-dose isotretinoin with a control group of 18 patients not taking isotretinoin reported no hypertrophic scarring or keloids following 2 to 7 fractionated nonablative

1550-nm erbium laser treatments for acne scarring. On the basis of a quantitative global acne scarring classification, the group taking low-dose isotretinoin showed a more effective (but not statistically significant) response.<sup>34</sup>

There are limited reports of complications experienced by patients receiving systemic isotretinoin during treatment. In a retrospective study of 110 patients (100 of whom underwent microneedling, CO<sub>2</sub> laser, or microneedle radiofrequency; half of the patients were taking isotretinoin), 2 patients experienced postinflammatory hyperpigmentation. Otherwise, there was no difference in wound healing and no evidence of atypical scarring in either group.<sup>30</sup> Mahadevappa et al<sup>11</sup> reported no incidences of keloid formation, hypertrophic scarring, or delayed healing following 102 fractional erbium:yttrium-aluminum-garnet (Er:YAG) laser resurfacing procedures, 19 fractional CO<sub>2</sub> laser resurfacing procedures, and 19 full-face CO<sub>2</sub> laser resurfacing procedures in patients concomitantly taking isotretinoin or who had recently completed therapy. All cases of postinflammatory pigmentation (15) or prolonged erythema (1) resolved without further sequelae.<sup>11</sup> Last, a single patient was spot treated with 3 modalities (a 1540-nm diode nonablative fractional laser, an Er:YAG 2940-nm fractional ablative laser, and an Er:YAG 2940-nm laser in fully ablative mode) while taking isotretinoin. On biopsy 6 months later, the patient was noted to have normal healing at both fractional nonablative and fractional ablative sites, but had developed a scar at the fully ablative treatment site.<sup>37</sup> This finding may be explained by the different wound healing response seen with use of a fully ablative laser compared with the fractionated modalities; fully ablative laser is nearly analogous to mechanical dermabrasion performed

Table 4. Summary of Evidence of Laser Procedures in the Setting of Isotretinoin Use

| Source                                       | Trial Design                           | Patients, No. | Level of Evidence | Isotretinoin Use                                     | Isotretinoin Dose                       | Type of Laser  | Outcome  |
|--|--|---------------|-------------------|--|---|--|--|
| Zachariae, <sup>6</sup> 1988                 | Case series                            | 1             | 4                 | Concomitant  | 60 mg                                   | Argon  | Development of keloids   |
| Bernestein and Geronemus, <sup>24</sup> 1997 | Case report                            | 1             | 5                 | Concomitant  | Unspecified                             | PDL 585 nm   | Development of keloids   |
| Khatri, <sup>25</sup> 2004                   | Case series                            | 7             | 4                 | Concomitant  | 20-80 mg                                | Diode 810 nm   | Nonscarring bullae in 1 patient (resolved), otherwise normal healing (36 procedures)   |
| Cassano et al, <sup>26</sup> 2005            | Case series                            | 6             | 4                 | Concomitant  | 0.5-1 mg/kg, decreased to 0.3-0.5 mg/kg | Diode 810 nm   | Normal healing (each patient underwent 4-9 treatments)   |
| Khatri and Garcia, <sup>27</sup> 2006        | Case series                            | 6             | 4                 | Concomitant  | 40-80 mg                                | Long-pulse flash lamp  | Normal healing (25 procedures)   |
| Khatri, <sup>28</sup> 2009                   | Case series                            | 11            | 4                 | Concomitant  | 0.5 mg/kg                               | Nd:YAG 1064 nm   | Normal healing (131 procedures)  |
| Leal and Cantu, <sup>31</sup> 2011           | Prospective cohort                     | 60            | 2                 | Concomitant (30 patients); >6 mo prior (30 patients) | 20 mg, average duration 11.4 mo         | Fractionated erbium  | Normal healing in both groups (each patient underwent a mode of 5 procedures)  |
| Kingsley et al, <sup>32</sup> 2012           | Case report                            | 1             | 5                 | 4 mo prior   | "Complete 6 month course"               | Fractionated CO <sub>2</sub>   | Normal healing (facial resurfacing)  |
| Patwardhan et al, <sup>29</sup> 2012         | Opinion                                | NA            | 5                 | Concomitant  | Unspecified                             | Alexandrite, Nd:YAG, erbium  | Normal healing   |
| Park et al, <sup>33</sup> 2013               | Case report                            | 1             | 5                 | "Immediately" prior                                  | 20 mg for 6 wk                          | Ultrapulse CO <sub>2</sub>   | Clearance of multiple eccrine hidrocystomas, normal healing  |
| Yoon et al, <sup>34</sup> 2014               | High-quality randomized clinical trial | 35            | 1                 | Concomitant  | 10 mg                                   | Erbium 1550 nm   | Normal healing (108 procedures)  |
| Chandrashekar et al, <sup>30</sup> 2014      | Retrospective cohort                   | 110           | 3                 | Concomitant  | 0.5 mg/kg/d                             | CO <sub>2</sub> (25 sessions); Nd:YAG 1064 nm, IPL, diode 980 nm   | PIH in 3 patients (2 taking isotretinoin), otherwise normal healing  |
| Kim et al, <sup>35</sup> 2014                | Case series                            | 20            | 4                 | Concomitant, or 4 weeks prior                        | 10-40 mg                                | CO <sub>2</sub> fractional ablative  | Normal healing (each patient underwent 1-6 procedures)   |
| Noh et al, <sup>36</sup> 2014                | Case report                            | 1             | 5                 | Immediately following                                | 150 mg/kg                               | CO <sub>2</sub>  | Normal healing; no recurrence of sebaceous hyperplasia   |
| Khatri et al, <sup>37</sup> 2015             | Case report                            | 1             | 5                 | Concomitant  | 80 mg                                   | Nonablative fractional; 1540 nm, ablative fractional (erbium:YAG 2940 nm); fully ablative (erbium:YAG 2940 nm)   | Nonablative and ablative fractional with normal healing; scar development following fully ablative                                     |
| Mahadevappa et al, <sup>11</sup> 2016        | Prospective cohort                     | 71            | 2                 | Concomitant or prior to                              | 10-40 mg                                | Laser hair procedures: long-pulsed Nd:YAG, IPL, long-pulsed diode; fractional ablative laser procedures: fractional Er:YAG (2940 nm, 100 J), fractional CO <sub>2</sub> (30 mJ), full-face CO <sub>2</sub> (3-mm spot, ultrapulse, 500 Hz, 250 μs) | 26 Laser hair procedures healed normally; 141 fractional ablative procedures resulted in 15 incidences of PIH, 1 of transient erythema |

Abbreviations: CO<sub>2</sub>, carbon dioxide; Er, erbium; IPL, intense pulsed light; NA, not applicable; Nd, neodymium-doped; PDL, pulsed dye light; PIH, postinflammatory hyperpigmentation; YAG, yttrium aluminum garnet.

in the 1980s and as such is rarely chosen by laser scar experts when fractional ablative and nonablative lasers are available (Table 4).

#### Consensus Recommendation

There is insufficient evidence to delay fractional ablative and nonablative laser treatment for patients who are currently taking or have recently completed isotretinoin treatment. Based on limited evidence, fully ablative laser procedures are not recommended in the setting of recent isotretinoin use. Additional prospective, well-controlled clinical trials are recommended (Table 2).

## Discussion

After objectively reviewing the published body of literature on the topic, this group of experts did not find sufficient, compelling evidence to support the current recommendation to delay manual dermabrasion, superficial chemical peels, cutaneous surgery, laser hair removal, fractional ablative, and fractional nonablative laser resurfacing for patients who are concomitantly taking or for 6 to 12 months following isotretinoin therapy. The reports reviewed in this article suggest that these specific procedures may indeed be safe

in the setting of recent isotretinoin use, and additional high-quality prospective studies are recommended. On the basis of the available evidence to date, mechanical dermabrasion and fully ablative laser procedures are not recommended in the setting of isotretinoin use at this time (Table 2). As a secondary recommendation, the well-known result of moderately to severely inflammatory acne is disfiguring, life-altering scarring, which should be treated as soon as possible. The current practice of avoiding procedural interventions for 6 to 12 months in patients treated with systemic isotretinoin for moderately to severely inflammatory acne is in direct conflict with current approaches to early intervention of scars and effectively delays treatment for many patients who experience the physical and mental sequelae of acne scarring.

For more than 3 decades, many clinicians have delayed or avoided a variety of procedural interventions for patients treated with systemic isotretinoin on the basis of a small number of case reports of delayed healing and scar formation. In our consensus-based assessment, these initial cases presented a hypothesis to be tested, rather than the foundation for medical dogma on which more than 30 years of clinical practice was built. Since the 1980s, the body of literature has grown and procedural interventions such as scar-ameliorating technology afforded by fractional ablative laser resurfacing have

evolved, further widening the research-practice gap. This gap may be explained by the phenomenon of *medical evidence evaluation bias*, wherein physicians are more willing to abandon a potentially harmful practice with little evidence of harm than to adopt a potentially beneficial one.<sup>38</sup> This bias was illustrated in a recent survey of nationally recognized experts in laser surgery regarding the treatment of patients taking or within 6 months of isotretinoin therapy. In this report, 70% of respondents affirmed that medical-legal concerns guided their decision making regarding this patient population, 69% were concerned about atypical or poor wound healing, 66% about scarring, and 49% about hypertrophic or keloidal scarring, despite 76% having never seen any complications in their own clinical practice.<sup>39</sup>

## Conclusions

With the information presented in this article, physicians may have an evidence-based discussion with patients regarding the known risk of cutaneous surgical procedures in the setting of systemic isotretinoin treatment. For some patients and some conditions, an informed decision may lead to earlier and potentially more effective interventions.

### ARTICLE INFORMATION

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### REFERENCES

1. Zaenglein AL, Thiboutot DM. Acne vulgaris. In: Bologna JL, Jorizzo JL, Schaffer JV, eds. *Dermatology*. 3rd ed. Philadelphia, PA: Elsevier; 2012:558.
2. Fabbrocini G, Elston DM. Chemical peels. Updated June 30, 2015. eMedicine website. <http://emedicine.medscape.com/article/1829120-overview#a3>. Accessed June 17, 2016.

3. American Academy of Dermatology. Isotretinoin: recommendations. <https://www.aad.org/practicecenter/quality/clinical-guidelines/acne/isotretinoin>. Accessed June 17, 2016.
4. Roenigk HH Jr, Pinski JB, Robinson JK, Hanke CW. Acne, retinoids, and dermabrasion. *J Dermatol Surg Oncol*. 1985;11(4):396-398.
5. Rubenstein R, Roenigk HH Jr, Stegman SJ, Hanke CW. Atypical keloids after dermabrasion of patients taking isotretinoin. *J Am Acad Dermatol*. 1986;15(2, pt 1):280-285.
6. Zachariae H. Delayed wound healing and keloid formation following argon laser treatment or dermabrasion during isotretinoin treatment. *Br J Dermatol*. 1988;118(5):703-706.
7. OCEBM Levels of Evidence Working Group. The Oxford Levels of Evidence 2. Oxford Centre for Evidence-Based Medicine. <http://www.cebm.net/index.aspx?o=5653>. Accessed February 3, 2017.
8. Katz BE, MacFarlane DF. Atypical facial scarring after isotretinoin therapy in a patient with previous dermabrasion. *J Am Acad Dermatol*. 1994;30(5, pt 2):852-853.
9. Bagatin E, dos Santos Guadanhim LR, Yarak S, Kamamoto CS, de Almeida FA. Dermabrasion for acne scars during treatment with oral isotretinoin. *Dermatol Surg*. 2010;36(4):483-489.
10. Picosse FR, Yarak S, Cabral NC, Bagatin E. Early chemabrasion for acne scars after treatment with oral isotretinoin. *Dermatol Surg*. 2012;38(9):1521-1526.
11. Mahadevappa OH, Mysore V, Viswanath V, et al. Surgical outcome in patients taking concomitant or recent intake of oral isotretinoin: a multicentric study-ISO-AIMS study. *J Cutan Aesthet Surg*. 2016;9(2):106-114.
12. Hernandez-Perez E, Khawaja HA, Alvarez TY. Oral isotretinoin as part of the treatment of cutaneous aging. *Dermatol Surg*. 2000;26(7):649-652.
13. Kar BR, Tripathy S, Panda M. Comparative study of oral isotretinoin versus oral isotretinoin + 20% salicylic acid peel in the treatment of active acne. *J Cutan Aesthet Surg*. 2013;6(4):204-208.
14. Gerber PA, Kukova G, Bölke E, Homey B, Diedrichson E. Severe hyperpigmentation and scarring following glycolic acid peel treatment in combination with low-dose isotretinoin. *Eur J Med Res*. 2014;19:60.
15. Ungarelli LF, Hetem CM, Farina Junior JA. Is it safe to operate on patients taking isotretinoin? *Aesthetic Plast Surg*. 2016;40(1):139-148.
16. Tan SR, Tope WD. Effect of acitretin on wound healing in organ transplant recipients. *Dermatol Surg*. 2004;30(4, pt 2):667-673.
17. Allen BC, Rhee JS. Complications associated with isotretinoin use after rhinoplasty. *Aesthetic Plast Surg*. 2005;29(2):102-106.
18. Sharma J, Thiboutot DM, Zaenglein AL. The effects of isotretinoin on wisdom tooth extraction. *J Am Acad Dermatol*. 2012;67(4):794-795.
19. Larson DL, Flugstad NA, O'Connor E, Kluesner KA, Plaza JA. Does systemic isotretinoin inhibit healing in a porcine wound model? *Aesthet Surg J*. 2012;32(8):989-998.
20. Huoh KC, Chang KW. Lip abscess associated with isotretinoin treatment of acne vulgaris. *JAMA Dermatol*. 2013;149(8):960-961.
21. Yew YW, Pan JY. Complete remission of recalcitrant genital warts with a combination approach of surgical debulking and oral isotretinoin in a patient with systemic lupus erythematosus. *Dermatol Ther*. 2014;27(2):79-82.
22. Wootton CI, Cartwright RP, Manning P, Williams HC. Should isotretinoin be stopped prior to surgery? a critically appraised topic. *Br J Dermatol*. 2014;170(2):239-244.
23. Landau M, Mesterman R, Ophir J, et al. Clinical significance of markedly elevated serum creatine kinase levels in patients with acne on isotretinoin. *Acta Derm Venereol*. 2001;81(5):350-352.
24. Bernstein LJ, Geronemus RG. Keloid formation with the 585-nm pulsed dye laser during isotretinoin treatment. *Arch Dermatol*. 1997;133(1):111-112.
25. Khatri KA. Diode laser hair removal in patients undergoing isotretinoin therapy. *Dermatol Surg*. 2004;30(9):1205-1207.
26. Cassano N, Arpaia N, Vena GA. Diode laser hair removal and isotretinoin therapy. *Dermatol Surg*. 2005;31(3):380-381.
27. Khatri KA, Garcia V. Light-assisted hair removal in patients undergoing isotretinoin therapy. *Dermatol Surg*. 2006;32(6):875-877.
28. Khatri KA. The safety of long-pulsed Nd:YAG laser hair removal in skin types III-V patients during concomitant isotretinoin therapy. *J Cosmet Laser Ther*. 2009;11(1):56-60.
29. Patwardhan M, Mehta B, Kangle S, Singh S. Isotretinoin and lasers: can they be used at the same time? *J Am Acad Dermatol*. 2012;66(4)(suppl 1):AB28.
30. Chandrashekar BS, Varsha DV, Vasanth V, Jagadish P, Madura C, Rajashekar ML. Safety of performing invasive acne scar treatment and laser hair removal in patients on oral isotretinoin: a retrospective study of 110 patients. *Int J Dermatol*. 2014;53(10):1281-1285.
31. Leal H, Cantu P. Fractional erbium laser during oral isotretinoin treatment. *J Am Acad Dermatol*. 2011;62(2)(suppl 1):AB18.
32. Kingsley M, Graber E, Bae-Harboe YSC. Treatment of acne scarring with ablative fractional laser resurfacing following isotretinoin therapy. *J Am Acad Dermatol*. 2012;66(4)(suppl 1):AB216.
33. Park HC, Kim EJ, Kim JE, Ro YS, Ko JY. Treatment of multiple eccrine hidrocystomas with isotretinoin followed by carbon dioxide laser. *J Dermatol*. 2013;40(5):414-415.
34. Yoon JH, Park EJ, Kwon IH, et al. Concomitant use of an infrared fractional laser with low-dose isotretinoin for the treatment of acne and acne scars. *J Dermatolog Treat*. 2014;25(2):142-146.
35. Kim HW, Chang SE, Kim JE, Ko JY, Ro YS. The safe delivery of fractional ablative carbon dioxide laser treatment for acne scars in Asian patients receiving oral isotretinoin. *Dermatol Surg*. 2014;40(12):1361-1366.
36. Noh S, Shin JU, Jung JY, Lee JH. A case of sebaceous hyperplasia maintained on low-dose isotretinoin after carbon dioxide laser treatment. *Int J Dermatol*. 2014;53(2):e151-e153.
37. Khatri KA, Iqbal N, Bhawan J. Laser skin resurfacing during isotretinoin therapy. *Dermatol Surg*. 2015;41(6):758-759.
38. Aberegg SK, Arkes H, Terry PB. Failure to adopt beneficial therapies caused by bias in medical evidence evaluation. *Med Decis Making*. 2006;26(6):575-582.
39. Prather HB, Alam M, Poon E, Arndt KA, Dover JS. Laser safety in isotretinoin use: a survey of expert opinion and practice. *Dermatol Surg*. 2017;43(3):357-363.