Dermatology Practical & Conceptual

Tretinoin for Photodamaged Facial Skin: Systematic Review and Meta-Analysis of Randomized Controlled Trials

Hsin-Yin Huang[1], Leon Tsung-Ju Lee[2,3,4]

1 Department of General Medicine, Taipei Medical University Hospital, Taipei Medical University, Taipei, Taiwan
2 Graduate Institute of Clinical Medicine, Taipei Medical University, Taipei, Taiwan
3 Department of Dermatology, Taipei Medical University Hospital, Taipei Medical University, Taipei, Taiwan
4 Department of Dermatology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

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Corresponding Author: Corresponding author: Leon Tsung-Ju Lee, Department of Dermatology, Taipei Medical University Hospital, No. 252, Wuxing St, Xinyi District, Taipei City, 110, Taiwan. ORCID ID: 0000-0001-6652-4390. E-mail: TJ.LEE.SKIN@GMAIL.COM

ABSTRACT

Introduction: Randomized controlled trials have suggested that tretinoin, a topical retinoid, can improve wrinkling in photodamaged skin; however, its overall effectiveness remains subject of debate.

Objectives: This study evaluated the efficacy and safety of tretinoin in treating facial wrinkles induced by photodamage.

Method: We systematically searched the PubMed, EMBASE, and Cochrane CENTRAL databases from their inception to 16 January 2024 to identify randomized controlled trials comparing topical tretinoin with vehicle treatments. Data were synthesized using a random effects model, and sensitivity analyses were performed to evaluate the robustness of the results in the presence of potential bias.

Results: This study identified eight trials (1,361 patients; median age range 29–76 years; average follow-up duration, 16 weeks to 2 years) that met the inclusion criteria. Compared with the vehicle, topical tretinoin significantly improved clinical signs of facial photodamage. Improvements were observed in both fine wrinkles (mean difference [MD]: 0.412; 95% confidence interval [CI]: 0.233–0.590; $P<0.001$) and coarse wrinkles (MD: 0.245; 95% CI: 0.119–0.370; $P<0.001$). Sensitivity analyses confirmed the robustness of these findings.

Conclusion: Topical tretinoin is a safe and effective treatment for fine and coarse facial wrinkles resulting from photodamage.

Introduction

The widespread use of social media has increased people's self-consciousness regarding their facial appearance. Many individuals consider facial skin aging to be undesirable and thus seek medical treatment for it. Such aging can be either intrinsic or extrinsic. Intrinsic aging results from unknown endogenous factors and genetically programmed skin cell deterioration, which can lead to epidermal or dermal atrophy. Skin affected by intrinsic aging typically exhibits thinning, decreased elasticity, and deeper expression lines. By contrast, extrinsic aging is caused by environmental factors, such as sun exposure. The extrinsic aging caused by chronic sun exposure is referred to as photoaging or photodamage, and it involves epidermal dysplasia, dermal damage, substantial elastosis, and collagen loss [1]. Facial manifestations of photoaging include fine and coarse wrinkles, irregular pigmentation, and changes in skin texture, elasticity, and thickness; they result from environmental influences rather than the natural progression of intrinsic aging [2].

Photodamage is associated with both undesirable cosmetic outcomes and pathological changes, including the development of benign and malignant tumors [2]. Many individuals seek treatment to address these aesthetic concerns and manage the underlying pathological problems related to photodamage to facial skin. Facial wrinkles are a common manifestation of skin aging and are one of the most prominent features of photoaging. Such wrinkles are generally categorized into two types: fine wrinkles and coarse wrinkles. Fine wrinkles appear as small folds in the superficial epidermal layers and are typically caused by skin dryness and photoaging. By contrast, coarse wrinkles are deeper folds within the dermal layer and primarily result from collagen and elastin loss.

Topical retinoids, which are derivatives of vitamin A, promote collagen synthesis and inhibit matrix metalloproteinase (MMP) activity by binding to and activating retinoic acid receptors. These receptors regulate the transcription of genes responsive to retinoic acid, thereby facilitating cell proliferation and differentiation. Topical retinoids are widely used to treat various dermatological conditions, including photoaging, acne vulgaris, psoriasis, cutaneous T-cell lymphoma, and Kaposi's sarcoma. Currently, six classes of topical retinoids are approved for clinical use: tretinoin (all-trans-retinoic acid), adapalene, tazarotene, trifarotene, alitretinoin, and bexarotene [3]. Among these, tretinoin is the only one that is effective at treating photoaging and wrinkles. Tretinoin operates through two distinct but synergistic molecular mechanisms. First, when applied prior to exposure to ultraviolet light, tretinoin inhibits activator protein-1 (AP-1) activity, which is a key driver of collagen-degrading MMPs. Second, topical application of tretinoin stimulates collagen synthesis by upregulating the expression of type I procollagen [3].

Unlike intrinsic aging, photoaging can be prevented by limiting sun exposure and applying sunscreen regularly [1,4,5]. Several alternative therapies have been developed for managing photoaging, including those involving non-retinoid topical agents, chemical peels, and laser resurfacing. Non-retinoid topical agents such as vitamin C, peptides, and growth factors have demonstrated potential in addressing photoaging; however, their effectiveness in reversing structural skin damage remains limited [9,10]. In addition, chemical peels and laser resurfacing may improve photoaging symptoms but are associated with risks such as irritation, prolonged recovery time, and outcome variability related to skin type [11,12]. Contemporary developments have indicated that injectable treatments, including treatment with hyaluronic acid and botulinum toxin, may help reduce the visibility of blood vessels in photodamaged skin [13,14]. This is particularly relevant for individuals with the atrophic photoaging phenotype, who commonly exhibit vascular features such as telangiectasias resulting from chronic sun exposure [13,15]. These injectables offer a noninvasive approach to addressing vascular changes commonly observed in the photoaged skin. In addition, individuals with the hypertrophic photoaging phenotype, characterized by deep and pronounced wrinkles, may benefit from injectables such as hyperdilute calcium hydroxylapatite, which stimulates collagen remodeling and improves overall skin texture [13,15-17]. These therapies are both cosmetic enhancers and targeted treatments for specific photoaging phenotypes. However, larger clinical trials are required to validate their efficacy and safety in treating photoaging and to clarify their role in personalized approaches to skin aging.

Large-scale trials have demonstrated that topical tretinoin is a safe and effective means of reducing facial wrinkling, mottled hyperpigmentation, and skin roughness. Tretinoin has also been reported to partially reverse skin photodamage [1,2,4-8]. Although topical tretinoin may have adverse effects, it remains the most promising therapeutic option for photoaged skin.

Objective

The present systematic review and meta-analysis evaluated the efficacy and adverse effects of topical tretinoin in the treatment of facial wrinkles.

Methods

General Guidelines

This meta-analysis was conducted in accordance with the latest version of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines

[18]. The PROSPERO registration number of this study is CRD42024511094.

Search Strategy and Study Selection

One investigator (HH) conducted a systematic search of three electronic databases, namely, PubMed, Embase, and Cochrane CENTRAL, for randomized controlled trials by using the following keywords: (topical retinoid) OR (retinoic acid) OR (all-trans-retinoic-acid) AND (photoaging) OR (photodamaged) AND (improvement) AND (wrinkle). The search included all records from the inception of each database to 16 January 2024. The complete search strategy is outlined in Supplementary Table S1. All identified trials were recorded in an Excel spreadsheet for review by a second investigator (LTL).

Two investigators (HH and LTL) independently screened the titles and abstracts of the retrieved studies for eligibility, and any discrepancies were resolved through discussion. Only full-text articles published in English were included.

Eligibility Criteria: Inclusion and Exclusion Criteria

The inclusion criteria for the trials were as follows: i) randomized, vehicle-controlled design; ii) use of tretinoin in a single formulation with variations in dosage, base, and application method as the primary treatment for photoaging; iii) evaluation of tretinoin's effects on facial skin wrinkles (fine wrinkles, coarse wrinkles, or both), with results reported as percentage improvements in wrinkle appearance; iv) inclusion of participants aged 18 years or older with mild, moderate, or severe skin photodamage.

In trials that employed multiple treatment dosages, data extraction was performed separately for each dosage to ensure analytical precision. Percentage improvements in wrinkle appearance were individually recorded for each dosage group. When trials reported aggregated outcomes without providing dosage-specific data, the corresponding authors were contacted to obtain detailed information. If these data were unavailable, results were included in the meta-analysis on the basis of the most relevant available information, and sensitivity analyses were conducted to evaluate the potential impact of data inconsistencies.

The following types of studies were excluded: i) nonrandomized controlled trials; ii) trials without a vehicle control; iii) studies assessing photoaging outcomes other than facial wrinkles; iv) trials using treatment regimens other than topical tretinoin; v) studies lacking data on percentage improvements in wrinkle appearance following therapy. Detailed reasons for article exclusion are provided in Table S2.

Outcomes and Data Extraction

The first reviewer (HH) conducted the initial data extraction on the basis of the inclusion criteria and recorded the results in Excel spreadsheets and tables. The second reviewer (LTL) independently extracted the data and compared their results with those of the first reviewer, and any discrepancies were resolved through discussion. Extracted data included study design, baseline demographics, tretinoin intervention details, treatment duration, and primary, secondary, and tertiary outcome values.

The primary outcome of interest was the percentage improvement in wrinkle appearance (fine or coarse) from baseline to the endpoint, as assessed by professional investigators in the included trials. Data were extracted separately for each wrinkle type, and percentages were manually calculated when only the number of patients exhibiting improvement was reported [1,6]. All relevant data were included from trials that reported multiple results either because multiple treatment dosages were used [5,19] or because the study was conducted at multiple centers [2]. If data were missing in a study (e.g., when the effect on coarse wrinkling was reported as nonsignificant, but no supporting data were provided, as in Weinstein et al. [19]), the corresponding author was contacted through email to obtain the original data. The secondary outcome of interest was the overall improvement in facial wrinkling caused by photodamage, as self-assessed by participants. The primary outcome was objective, whereas the secondary outcome was subjective. Percentage improvements for both outcomes were extracted and are presented in Table S3. The tertiary outcome involved adverse events, and event rates were calculated and are reported using odds ratios (OR).

Study Quality and Risk of Bias Assessments

The quality of the included studies was independently assessed by two reviewers (HH and LTL) by using the Cochrane Risk of Bias Tool for Randomized Trials (version 2, RoB 2, London, UK). Six domains of bias were evaluated: i) randomization process; ii) intervention adherence; iii) missing outcome data; iv) outcome measurement; v) selective reporting; vi) overall risk of bias [20]. Each domain was rated as low risk, some concerns, or high risk. On the basis of these ratings, each trial was categorized as having a low risk of bias, some concerns, or a high risk of bias. Any disagreement between reviewers was resolved through discussion and until a consensus was reached.

Statistical Analysis

A random effects model was used to analyze the data through Comprehensive Meta-Analysis software (version 4, Biostat, Englewood, NJ, USA). A two-tailed p-value of <0.05 was considered significant.

The primary and secondary outcomes were quantified using mean differences (MD) with corresponding 95% confidence intervals (CI). The tertiary outcome was quantified using OR and their associated 95% CI. Heterogeneity among the included trials was evaluated using the I^2 and Cochran's Q statistics, with I^2 values of 30%, 50%, and 75% indicating moderate, substantial, and considerable heterogeneity, respectively [18]. To validate the robustness of the findings, sensitivity analyses were performed using the one-study-removal method. This approach is used to determine whether the exclusion of any single trial results in significant changes in the overall effect size [18]. Potential publication bias was evaluated using funnel plot analysis and Egger's regression tests.

Results

A total of 128 relevant randomized controlled trials were identified through the database search, of which eight met the inclusion criteria and were included in the qualitative and quantitative syntheses (Figure 1). These eight trials were published between 1988 and 2006. Their characteristics are summarized in Table 1 and Supplementary Table S4. Collectively, the trials enrolled 1,361 patients aged between 29 and 76 years. All trials were conducted in the United States, with the exception of one conducted in Australia. The baseline severity of photoaging among the participants ranged from mild to severe. The average follow-up duration varied from 16 weeks to two years. Study quality assessments are presented in Table S5, and detailed data on clinical improvements and patient-reported outcomes from all trials are provided in Table S3.

Primary Outcome: Improvement in Fine Facial Wrinkles After Treatment With Tretinoin Compared With a Vehicle

All eight trials assessed clinical improvement in fine wrinkles by comparing tretinoin treatment with a vehicle. A significant improvement in fine facial wrinkles was observed following tretinoin treatment (MD: 0.412; 95% CI: 0.233–0.590; $P<0.001$; $I^2=35.438\%$; Figure 2). Moderate heterogeneity was noted in the included trials. To examine the robustness of the findings, a sensitivity analysis was performed using the one-study-removal method; the significant effect of tretinoin on fine wrinkle improvement remained consistent ($P<0.001$; Figure S1). Exclusion of any individual trial did not affect the overall significance of the findings. However, Egger's test indicated potential publication bias in the studies evaluating improvements in fine wrinkles ($P<0.001$; Figure S2).

Primary Outcome: Improvement in Coarse Facial Wrinkles After Treatment With Tretinoin Compared With a Vehicle

Six trials, excluding those conducted by Olsen et al. [5] and Weinstein et al. [19], evaluated the efficacy of tretinoin in improving coarse facial wrinkles. Consistent with the findings for fine wrinkles, tretinoin treatment led to a significant improvement in coarse wrinkles (MD:0.245; 95% CI: 0.119–0.370; $P<0.001$; $I^2=0\%$; Figure 3). No significant heterogeneity was detected. In a sensitivity analysis using the one-study-removal method, the significant effect of tretinoin on coarse wrinkle improvement remained unchanged ($P<0.001$; Figure S3). In addition, Egger's test indicated no significant publication bias in the studies assessing improvements in coarse wrinkles ($P=0.457$; Figure S4).

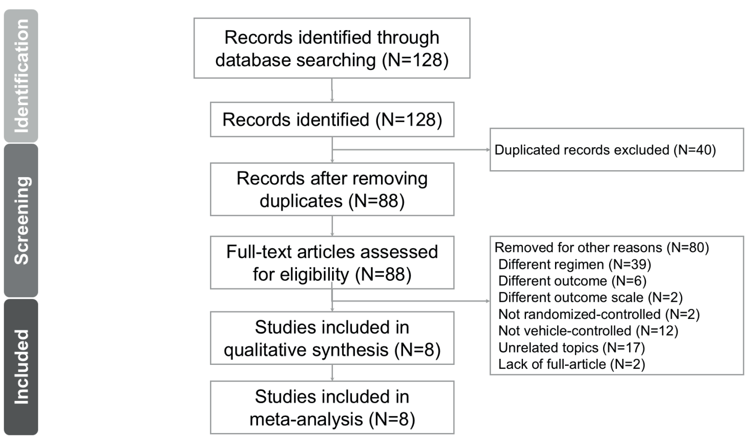

Figure 1. PRISMA flow diagram.

Table 1. Retrieved Trials Investigating the Effectiveness of Topical Retinoid Treatment in Improving Photodamage-Induced Wrinkles.

First author and year	Country	Population	Patient number (tretinoin/vehicle), N	Sex (male/female), N	Age [1]	Study design	Allocation concealment	Randomization	Funding/grants/support
Weiss 1988	USA	Healthy White patients	15/15	Sex not mentioned	50 (35–70)	RCT, double-blind	Not mentioned	Table of random numbers	- Ortho Pharmaceutical Corp. - Babcock Dermatologic Endowment
Weinstein 1991	USA	Healthy White patients	200/99	34/265	41 (29–50)	RCT, double-blind	Not mentioned	Randomization code	R. W. Johnson Pharmaceutical Research Institute
Olsen 1992	USA	Healthy White patients	224/72	Tretinoin 0.05%: 55/21 Vehicle: 50/22	42.5 (30–58)	RCT, double-blind	Double-blind tubes	Not mentioned	R. W. Johnson Pharmaceutical Research Institute
Andreano 1993	USA	White patients	17/17	Total: 28/6	41 (31–50)	RCT, double-blind	Not mentioned	Not mentioned	Ortho Pharmaceutical Corporation
Lowe 1994	Australia	Healthy White patients	62/63	Total: 115/10	46 (30–65)	RCT, double-blind	Not mentioned	Computer-generated randomization code	Janssen-Cilag Pty Ltd.
Nyirady 2001	USA	White patients	Study 1: 77/83 Study 2: 82/86	Study 1[2]: Tretinoin 0.02%: 78/12 Vehicle: 80/9 Study 2[2]: Tretinoin 0.02%: 79/10 Vehicle: 80/10	Study 1: 58.4 (45–69) Study 2: 58.6 (43–70)	RCT, double-blind	Not mentioned	Not mentioned	Ortho Dermatological Division of Ortho-McNeil Pharmaceutical, Inc.
Kang 2005	USA	Healthy patients	101/103	Tretinoin 0.05%: 91/10 Vehicle: 92/11	Tretinoin: 63.2 (40–76) Vehicle: 62.4 (43–75)	RCT, double-blind	Not mentioned	Computer-generated randomization lists	OrthoNeutrogena
Weiss 2006	USA	Healthy White patients	22/23	Total: 44/1	(38–73)	RCT, double-blind	Not mentioned	Not mentioned	OrthoNeutrogena

RCT: randomized controlled trial. USA: United States of America. [1] Age is presented as means (ranges) or as (ranges) only. [2] Sex was assessed in studies evaluating safety instead of efficacy.

Study name	Difference in means	Lower limit	Upper limit	p-Value	Relative weight
Weiss 1988 F	0.930	0.590	1.270	0.000	12.99
Weinstein 1991 F0.05%	0.320	-0.287	0.927	0.302	6.40
Weinstein 1991 F0.01%	0.220	-0.439	0.879	0.513	5.65
Olsen 1992 F0.05%	0.190	-0.408	0.788	0.533	6.55
Olsen 1992 F0.01%	0.020	-0.629	0.669	0.952	5.79
Olsen 1992 F0.001%	0.110	-0.435	0.655	0.692	7.48
Andreano 1993 F	0.580	0.199	0.961	0.003	11.59
Lowe 1994 F	0.320	-0.240	0.880	0.263	7.20
Nyirady 2001 F1	0.290	-0.136	0.716	0.182	10.26
Nyirady 2001 F2	0.170	-0.436	0.776	0.582	6.43
Kang 2005 F	0.210	-0.368	0.788	0.476	6.88
Weiss 2006 F	0.710	0.364	1.056	0.000	12.79
Pooled	0.412	0.233	0.590	0.000	

(Statistics for each study)

Q value = 17.038, df = 11 (P = 0.107), I² = 35.438

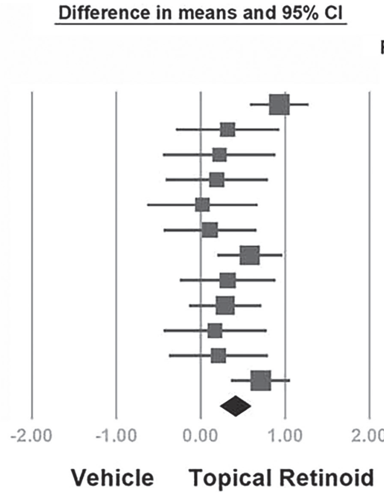

Figure 2. Forest plot illustrating the effects of topical tretinoin on fine wrinkles on photodamaged facial skin compared with placebo (vehicle). This figure summarizes the results of clinical studies evaluating the effectiveness of tretinoin, a topical retinoid, in reducing fine facial wrinkles caused by sun damage. The plot reveals that tretinoin led to a significantly greater improvement in wrinkle appearance than the placebo treatment did. (CI = confidence interval; F = fine wrinkles)

Study name	Difference in means	Lower limit	Upper limit	p-Value	Relative weight
Weiss 1988 C	0.400	0.137	0.663	0.003	22.79
Andreano 1993 C	0.350	0.036	0.664	0.029	15.99
Lowe 1994 C	0.170	-0.493	0.833	0.615	3.60
Nyirady 2001 C1	0.180	-0.261	0.621	0.424	8.12
Nyirady 2001 C2	0.160	-0.182	0.502	0.360	13.48
Kang 2005 C	0.070	-0.438	0.578	0.787	6.13
Weiss 2006 C	0.170	-0.060	0.400	0.147	29.90
Pooled	0.245	0.119	0.370	0.000	

(Statistics for each study)

Q value = 2.993, df = 6 (P = 0.810), I² = 0.000

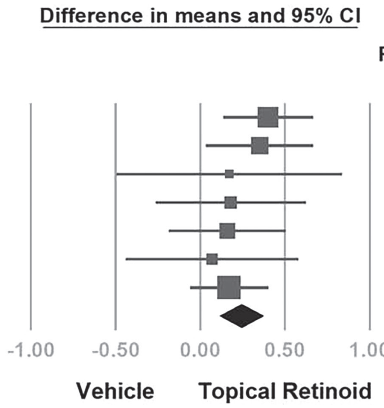

Figure 3. Forest plot illustrating the effects of topical tretinoin on coarse wrinkles in photodamaged facial skin compared with placebo (vehicle). This figure summarizes the results of clinical studies evaluating the effectiveness of tretinoin, a topical retinoid, in reducing coarse facial wrinkles caused by sun damage. The plot reveals that tretinoin led to a significantly greater improvement in wrinkle appearance than the placebo treatment did (C = coarse wrinkles; CI = confidence interval).

Secondary Outcome: Patient Self-Assessments of Overall Improvement in Photodamage Severity of Facial Skin After Treatment With Tretinoin Compared With a Vehicle

Six of the eight included trials reported data on patient self-assessments of overall improvement in photoaging, including with respect to skin appearance and texture, following treatment with tretinoin compared with a vehicle [2,5-8,19]. Patients who received tretinoin provided significantly higher ratings for overall improvement (MD: 0.270; 95% CI: 0.033–0.508; P=0.026; I^2=0%; Figure S5). The sensitivity analysis revealed consistent results (P=0.026; Figure S6). No significant heterogeneity was observed among the trials. Additionally, Egger's test revealed no significant publication bias in studies evaluating patient self-assessments (P=0.284; Figure S7).

Tertiary Outcome: Adverse Event Rates Associated With Treatment

Among the 1,361 patients included in the trials, 822 received tretinoin treatment. A total of 492 treatment-related adverse events were reported in this group. Meta-analysis of adverse event rates revealed a significant increase in the likelihood of experiencing adverse events following tretinoin treatment

(OR: 3.140; 95% CI: 1.819–5.419; $P<0.001$; $I^2=73.261\%$; Figure S8).

Discussion

This systematic review and meta-analysis is the first to comprehensively evaluate both the safety and the efficacy of tretinoin in treating photodamage-induced facial wrinkles. The results revealed significant improvements in both fine and coarse facial wrinkles following tretinoin treatment compared with after the use of a vehicle. These findings remained robust in sensitivity analyses conducted using the one-study-removal method. In our meta-analysis, no significant heterogeneity was noted among studies assessing the efficacy of tretinoin for coarse wrinkles, and only moderate heterogeneity was observed in those evaluating fine wrinkles, suggesting consistent therapeutic benefits across different patient populations and study designs. This homogeneity may be attributed to the relatively standardized treatment protocols and objective efficacy measurements, such as global photographic assessment and lesion count reduction.

Photoaging is an extrinsic factor that contributes to the development of wrinkles. Ultraviolet light exposure leads to histologic damage to the skin, including epidermal dysplasia and atrophy, substantial elastosis in the dermis, increased melanocyte activity, and high levels of glycosaminoglycans and inflammatory infiltrates [1,4]. Additionally, the degradation of collagen and accumulation of elastotic material in the dermal extracellular matrix reduce mechanical support to the epidermis [4], ultimately contributing to photodamage-induced facial wrinkling [7].

Five of the eight trials included in this review assessed histological changes in skin biopsies before and after tretinoin treatment [1,4,5,7,19]. Across these studies, tretinoin consistently induced epidermal thickening, compaction of the stratum corneum, granular layer expansion, and reduced melanin content, changes associated with improved skin texture and reduced wrinkle appearance [1,5,7,19]. One study also reported increased levels of procollagen 1 C-terminal (PIC) and N-terminal (SP1) levels, suggesting enhanced collagen synthesis as a mechanism for wrinkle reduction [4].

The epidermal response observed following topical tretinoin application is mediated by well-established biochemical pathways in keratinocytes. Tretinoin regulates epidermal cell proliferation and differentiation by interacting with cellular retinoic acid–binding proteins, which function as receptors for all-trans-retinoic acid. Upon binding to specific cytosolic receptors, tretinoin translocates to the nucleus, where it modulates protein synthesis and enhances the features of photodamaged skin [1,5].

Tretinoin exerts its primary therapeutic effects through retinoic acid receptors (RARs), with RAR-γ being the predominant isoform in human skin [21]. The binding of tretinoin to RARs triggers a cascade of gene expression that regulates keratinocyte proliferation and differentiation [21]. Animal studies have demonstrated that RAR-γ activity, in coordination with retinoid X receptor alpha (RXRα), is essential to tretinoin-induced epidermal thickening [22]. Several molecular biomarkers have been identified as potential predictors of treatment response, including RAR-γ expression, Ki-67, and epidermal growth factor receptor (EGFR) pathway activation. Ki-67 is a nuclear protein expressed during active phases of the cell cycle, making it a widely used marker of cellular proliferation [23]. Increased Ki-67 expression following tretinoin treatment indicates increased keratinocyte turnover, which often correlates with visible improvements in skin appearance [23]. Additionally, tretinoin upregulates EGFR ligands such as amphiregulin (AR) and heparin-binding epidermal growth factor–like growth factor (HB-EGF), which further promote keratinocyte activity and epidermal hyperplasia [24]. These molecular effects support tretinoin's role in reversing photodamage and may guide personalized treatment strategies.

In the current analysis, in addition to the significant improvements in facial wrinkles noted by professional investigators, the study participants reported noticeable enhancements in the overall appearance and texture of their photodamaged skin following treatment ($P=0.026$). The sensitivity analysis conducted using the one-study-removal method confirmed the robustness of these findings. The significant improvement in the patient self-assessments further confirms the therapeutic effect of tretinoin on both objective and subjective measures. The results confirm that tretinoin significantly improves fine and coarse wrinkles; however, its impact on quality of life is also a critical concern. The patient-reported outcomes in this study indicated improvements in skin appearance and texture, suggesting potential psychological and emotional benefits associated with treatment.

Although tretinoin demonstrated significant efficacy in improving photodamaged skin ($P<0.001$), patients were frequently affected by adverse reactions. Across the included trials, individuals receiving tretinoin experienced various forms of cutaneous irritation, such as dryness, erythema, peeling, burning, and stinging, particularly during the initial weeks of treatment [1,2,4-8,19]. The severity of these effects was generally mild [2,4,7,8,19] or mild-to-moderate [5,6]. It is worth noting that considerable heterogeneity was observed in the tertiary outcome related to adverse events. This variability is likely attributable to differences in study duration, tretinoin concentrations, vehicle formulations, and the subjective nature of reporting symptoms such as irritation or dryness, which are heavily influenced by individual tolerance and study-specific factors. In some cases, these adverse reactions were sufficiently bothersome to result in temporary discontinuation or modification of the treatment regimen. Previous studies have suggested that irritation may be mitigated by gradually escalating the dose, using moisturizers concurrently, or applying topical corticosteroids for short-term relief [1,5,6]. Nonetheless, further research is required to optimize treatment protocols that improve long-term adherence without reducing therapeutic efficacy. Patient adherence remains a key challenge in tretinoin treatment because of the high frequency of adverse effects. Because patient adherence is a critical determinant of clinical outcomes, education and individualized management strategies are essential. Ensuring that patients anticipate and are able to manage transient irritation may enhance treatment persistence. Additional investigations identifying alternative formulations, such as those with lower tretinoin concentrations or newer retinoid derivatives with improved tolerability, could help address this.

In the current study, common adverse reactions to topical tretinoin were generally resolved with continued use or appropriate supportive care. Some have speculated that the irritation and inflammation induced by topical retinoids may contribute to wrinkle improvement because mild swelling could temporarily reduce the appearance of wrinkles [1]. However, findings from the trial by Weiss et al. [1] indicated that no edema was observed in post-treatment skin biopsy specimens, and no improvement in photoaging was noted in areas affected by tretinoin-induced dermatitis. Additional controlled trials reported that the application of other irritants, such as salicylic acid, did not produce similar improvements in photodamaged skin [7]. Moreover, Olsen et al. [5] identified no clinical correlation between irritation and treatment response. In that study, only half of the patients who experienced satisfactory-to-excellent improvement rated their irritation level as 5 or higher on a 9-point grading scale [5].

The long-term safety of tretinoin treatment was assessed in a trial conducted by Kang et al. [4]. Over a 2-year treatment period, minimal histological changes were observed in the skin of most patients (≥85%). The evaluated histological parameters included keratinocytic dysplasia, melanocytic dysplasia, dermal elastosis, and the stratum corneum. The findings demonstrated that topical tretinoin is safe for long-term use of up to two years and does not induce cellular atypia within that timeframe.

In addition to retinoids, agents such as peptides, antioxidants, and growth factors have garnered interest for their anti-aging properties. Peptides and growth factors, in particular, have demonstrated an ability to stimulate collagen production and improve photodamaged skin with minimal adverse effects [9,10,25,26]. However, many of the studies that support the use of these treatments are limited by small sample sizes and nonrandomized designs, which reduce the overall strength of the evidence because of the potential for bias [9,10]. Cosmetic procedures such as microneedling and laser therapy, either as standalone treatments or in combination with tretinoin, are also effective options for individuals seeking rejuvenation strategies with reduced irritation. Although tretinoin remains a widely used and effective intervention, emerging therapies may offer advantages over tretinoin in terms of efficacy and tolerability. Future research should include larger, long-term clinical trials to compare these therapies and identify optimal treatment regimens for managing photoaging.

To assist clinicians in translating these findings into daily practice, Table 2 summarizes practical considerations and recommendations for the safe and effective use of topical tretinoin in treating photodamaged facial skin.

Limitations

Our study has several limitations. First, the randomized controlled trials included in this meta-analysis exhibited variability in terms of their design and methodology, including differences in treatment formulation, dosage, and duration. These inconsistencies may have contributed to heterogeneity in the reported outcomes and could affect the interpretability of their findings. Although this study standardized outcome measurements by using percentage improvements in wrinkle appearance, the initial assessment scales varied across the trials. Additional variations in dosages, treatment durations, and drug vehicles may have influenced the observed heterogeneity in fine wrinkle outcomes and affected the consistency of estimated treatment effects. To address this, we employed a random effects model and conducted sensitivity analyses. Second, the potential for reporting or publication bias cannot be excluded. Publication bias occurs when positive results are more likely to be published than are negative or null findings, leading to an overestimation of treatment efficacy. In our analysis, evidence of publication bias was observed in trials assessing improvements in fine wrinkles, suggesting that these results should be interpreted with caution. Third, most included trials lacked long-term follow-up data. The longest treatment duration reported was two years, thus limiting our ability to evaluate the sustained effectiveness and long-term safety of topical retinoids for treating fine and coarse wrinkles.

Although patient-reported outcomes indicated satisfaction with tretinoin treatment, the trials did not capture specific quality-of-life feedback, such as that regarding skin comfort or psychological and emotional impacts. Future studies should incorporate validated QoL instruments, such as the Dermatology Life Quality Index, to better assess the real-world impact of tretinoin therapy.

Table 2. Practical Takeaways for Clinicians: Topical Tretinoin Use.

Clinical Consideration	Recommendation
Patient Selection Based on Photodamage Severity	• Select patients with **mild-to-moderate photodamage** for best response • Use a **standardized 9-point photodamage scale**[1] to assess severity • **Avoid initiating** tretinoin in patients with severe photodamage until **skin barrier is optimized**
Initiation in Sensitive or Reactive Skin	• Start with **lower concentration** (e.g., ≤0.02%) • **Titrate gradually** as tolerated • Reduce application frequency to **every other night** if needed • Help improve **adherence** and **reduce discontinuation** due to irritation
Strategies for Mitigating Adverse Reactions	• Apply **moisturizer** before or after tretinoin to minimize irritation • Educate patients on **adaptation period** (typically 2–4 weeks) • Avoid **harsh skincare products** (e.g., alcohol-based toners, exfoliants) • Use **short-term topical corticosteroids** for severe irritation to control inflammation without reducing efficacy

[1] Please refer to: C.E. Griffiths, T.S. Wang, T.A. Hamilton, J.J. Voorhees, C.N. Ellis, A photonumeric scale for the assessment of cutaneous photodamage, *Arch Dermatol*, 128 (1992) 347-351. PMID: 1550366.

Despite these limitations, our findings indicate that tretinoin, across various dosages and treatment durations, significantly improves fine and coarse wrinkles on photodamaged facial skin. Findings of patient satisfaction, as reflected in subjective assessments, further support the clinical value of tretinoin treatment. However, such treatment's association with skin irritation highlights a need for continued research to determine optimal dosing strategies and to develop approaches to minimizing adverse reactions, which can improve the efficacy and safety of treatment.

Conclusion

Tretinoin treatment has been demonstrated to significantly improve facial wrinkling caused by photodamage, including both fine and coarse wrinkles, relative to a vehicle. Although some patients experience skin irritation in response to treatment, overall satisfaction with the improvements in photoaging was frequently reported following tretinoin therapy. These findings underscore the therapeutic value of topical tretinoin in addressing visible signs of photoaging. However, because of the potential for irritation and the variability in individual responses, additional research should be conducted to develop safer and more effective tretinoin formulations that better accommodate patient needs. Long-term follow-up studies are also necessary to evaluate the durability of treatment effects and to assess the long-term safety of topical retinoids. Additionally, such studies should investigate the broader impact of tretinoin on overall skin health and provide research that contributes to the development of evidence-based guidelines for its integration into clinical skin care regimens.

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