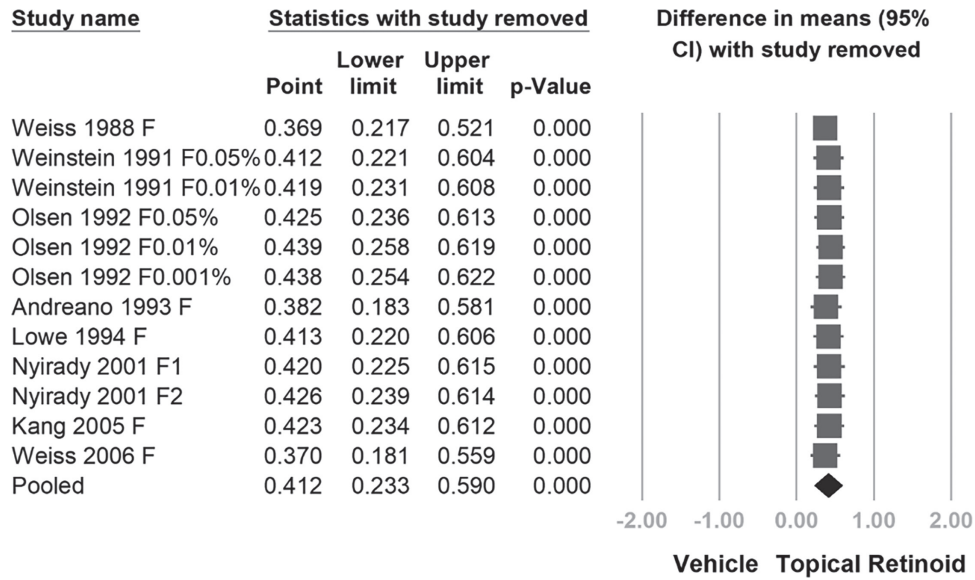
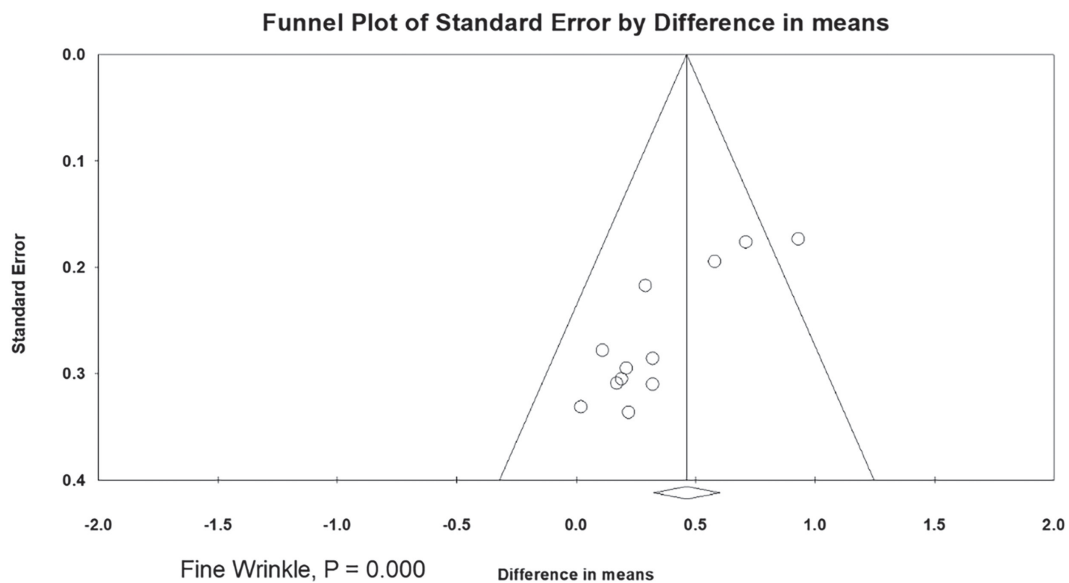


## Supplementary file



**Figure S1.** Sensitivity analysis using the one-study-removal method. The results indicated a statistically significant improvement in facial fine wrinkling, even after removing any one of the included trials. CI: confidence interval. F: fine wrinkles.



**Figure S2.** Funnel plot of all eight trials that were included in the analysis of fine wrinkles. Egger's test revealed a p-value of 0.000, indicating some publication bias.

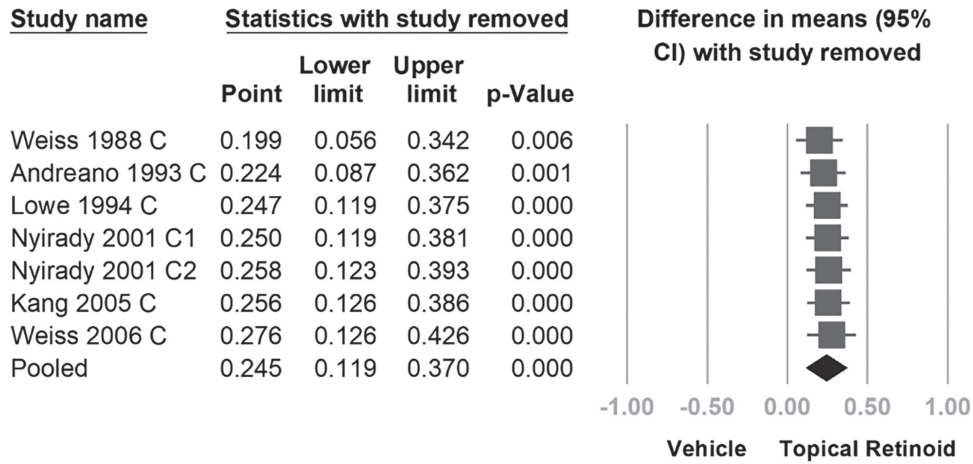


Figure S3. Sensitivity analysis using the one-study-removal method. The results indicated statistically significant improvement in facial coarse wrinkling even after removing any one of the included trials. CI: confidence interval. C: coarse wrinkles.

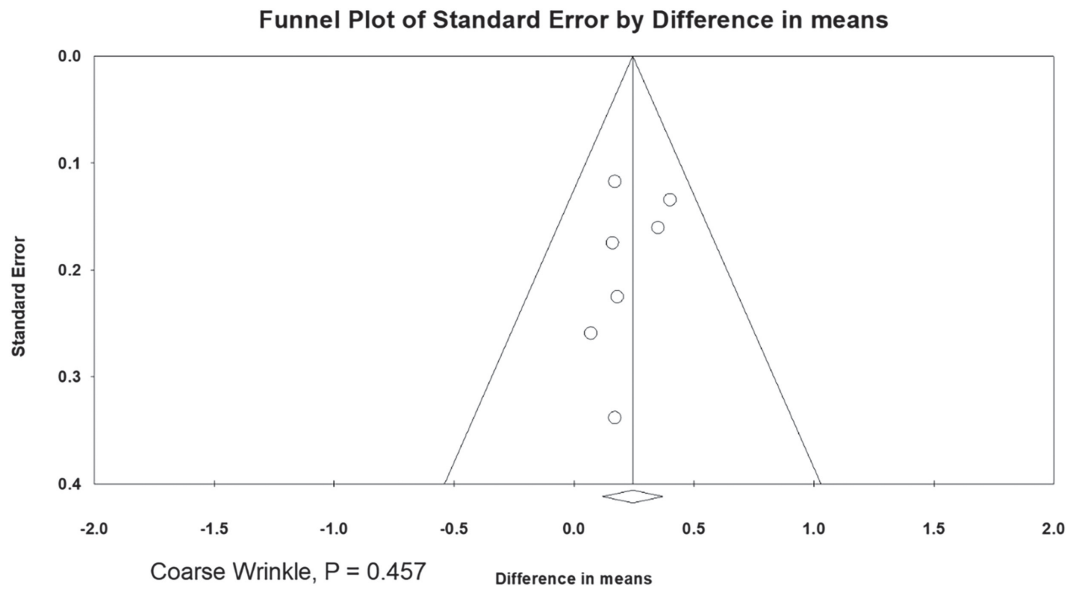


Figure S4. Funnel plot of six out of eight trials that were included in the analysis of coarse wrinkles. Egger's test revealed a p-value of 0.457, indicating no notable publication bias.

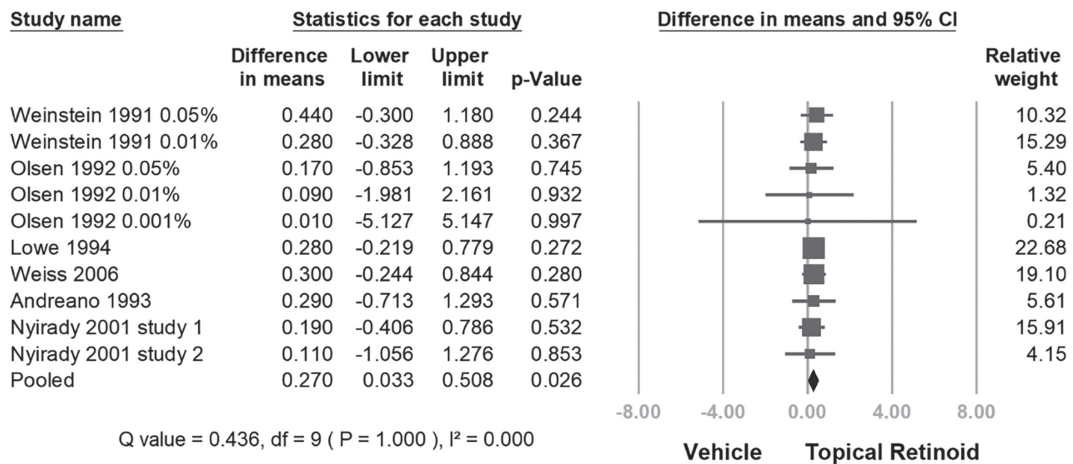


Figure S5. Forest plot of patient self-assessment of overall improvement of photodamaged skin from six relative trials. The statistically significant result revealed that patients favored the treatment effect of tretinoin over placebo. CI: confidence interval.

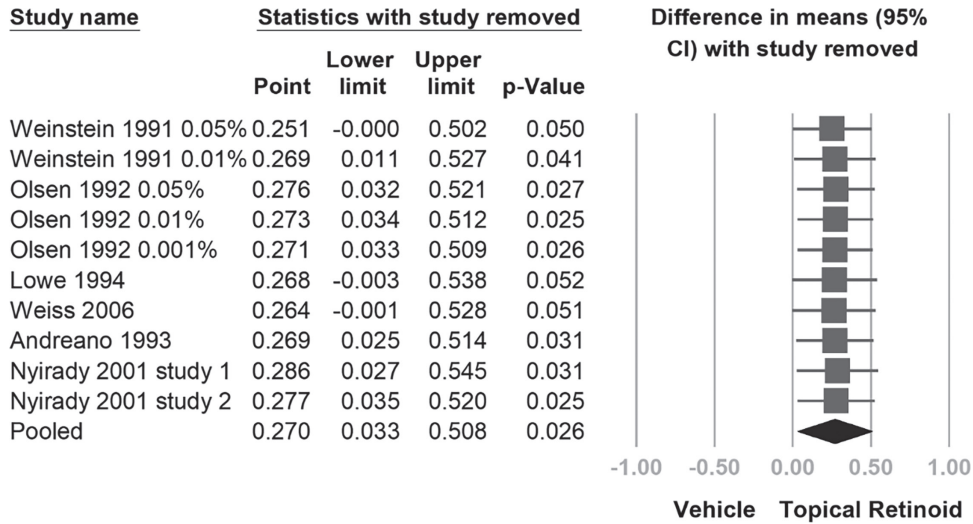


Figure S6. Sensitivity analysis of patient self-assessment of overall improvement of photodamaged skin using the one-study-removal method. The results indicated maintenance of significant improvement in overall photodamaged skin even after removing any one of the included trials. CI: confidence interval.

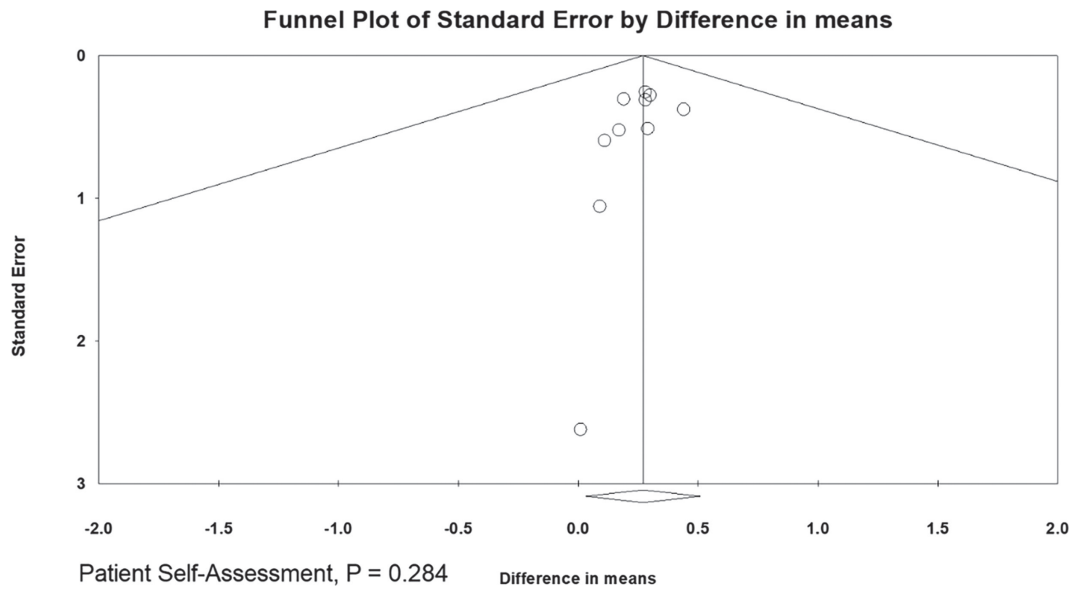


Figure S7. Funnel plot of six out of eight trials that were included in the analysis of patient self-assessment. Egger's test revealed a p-value of 0.284, indicating no notable publication bias.

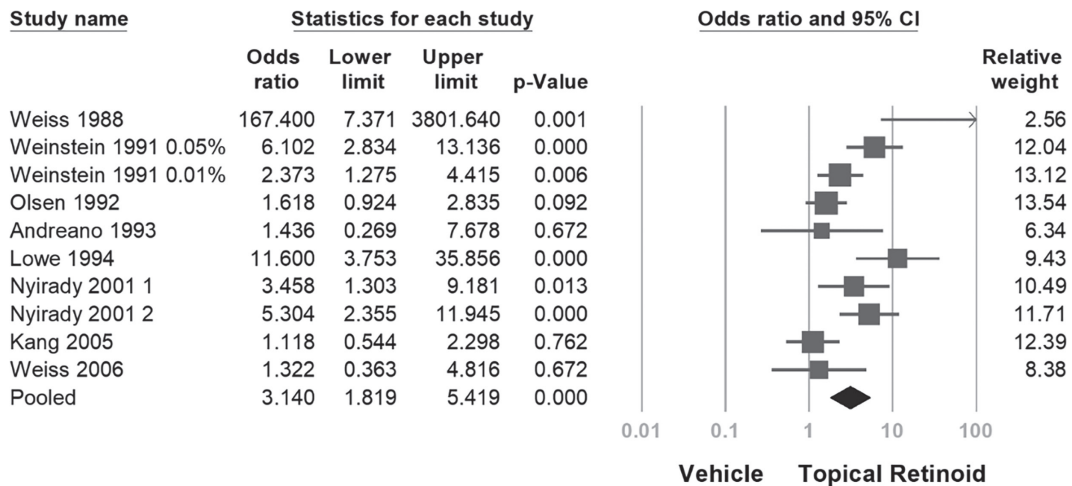


Figure S8. Forest plot of adverse events rate related to treatment: 492 out of 822 patients in the active treatment group with tretinoin experienced skin irritation. CI: confidence interval.

**Table S1. Keywords and Search Results in Different Databases.**

Database	Keyword	Filter	Date	Results
PubMed	((topical retinoid) OR (retinoic acid) OR (all-trans-retinoic-acid)) AND ((photoaging) OR (photodamaged)) AND ((improvement) AND (wrinkle))	Randomized Controlled Trial	16 January 2024	67
Embase	((topical retinoid) OR (retinoic acid) OR (all-trans-retinoic-acid)) AND ((photoaging) OR (photodamaged)) AND ((improvement) AND (wrinkle))	Randomized Controlled Trial	16 January 2024	26
Cochrane CENTRAL	((topical retinoid) OR (retinoic acid) OR (all-trans-retinoic-acid)) AND ((photoaging) OR (photodamaged)) AND ((improvement) AND (wrinkle))	Title Abstract Keyword	16 January 2024	35

**Table S2. Excluded Studies and Reasons for Exclusion.**

Citations	Reasons
Phillips TJ, Gottlieb AB, Leyden JJ, Lowe NJ, Lew-Kaya DA, Sefton J, Walker PS, Gibson JR; Tazarotene Cream Photodamage Clinical Study Group. Efficacy of 0.1% tazarotene cream for the treatment of photodamage: a 12-month multicenter, randomized trial. Arch Dermatol. 2002 Nov;138(11):1486-93. doi: 10.1001/archderm.138.11.1486. PMID: 12437455.	Different regimen (other topical retinoid; tazarotene)
Kang S, Leyden JJ, Lowe NJ, Ortonne JP, Phillips TJ, Weinstein GD, Bhawan J, Lew-Kaya DA, Matsumoto RM, Sefton J, Walker PS, Gibson JR. Tazarotene cream for the treatment of facial photodamage: a multicenter, investigator-masked, randomized, vehicle-controlled, parallel comparison of 0.01%, 0.025%, 0.05%, and 0.1% tazarotene creams with 0.05% tretinoin emollient cream applied once daily for 24 weeks. Arch Dermatol. 2001 Dec;137(12):1597-604. doi: 10.1001/archderm.137.12.1597. PMID: 11735710.	Different regimen (other topical retinoid; tazarotene)
Armstrong RB, Lesiewicz J, Harvey G, Lee LF, Spoehr KT, Zultak M. Clinical panel assessment of photodamaged skin treated with isotretinoin using photographs. Arch Dermatol. 1992 Mar;128(3):352-6. PMID: 1550367.	Different regimen (other topical retinoid; isotretinoin)
Bagatin E, Parada MO, Miot HA, Hassun KM, Michalany N, Talarico S. A randomized and controlled trial about the use of oral isotretinoin for photoaging. Int J Dermatol. 2010 Feb;49(2):207-14. doi: 10.1111/j.1365-4632.2009.04310.x. PMID: 20465648.	Different regimen (oral isotretinoin)
Griffiths CE, Russman AN, Majmudar G, Singer RS, Hamilton TA, Voorhees JJ. Restoration of collagen formation in photodamaged human skin by tretinoin (retinoic acid). N Engl J Med. 1993 Aug 19;329(8):530-5. doi: 10.1056/NEJM199308193290803. PMID: 8336752.	Different outcome (assessed collagen formation as primary outcome)
Gupta MA, Schork NJ, Ellis CN. Psychosocial correlates of the treatment of photodamaged skin with topical retinoic acid: a prospective controlled study. J Am Acad Dermatol. 1994 Jun;30(6):969-72. doi: 10.1016/s0190-9622(94)70119-9. PMID: 8188889.	Different outcome (assessed psychosocial aspect of treatment)
Bhawan J, Olsen E, Lufrano L, Thorne EG, Schwab B, Gilchrest BA. Histologic evaluation of the long term effects of tretinoin on photodamaged skin. J Dermatol Sci. 1996 Mar;11(3):177-82. doi: 10.1016/0923-1811(95)00432-7. PMID: 8785167.	Different outcome (assessed histological parameter)
Bhawan J, Gonzalez-Serva A, Nehal K, Labadie R, Lufrano L, Thorne EG, Gilchrest BA. Effects of tretinoin on photodamaged skin. A histologic study. Arch Dermatol. 1991 May;127(5):666-72. Erratum in: Arch Dermatol 1991 Sep;127(9):1382. PMID: 2024984.	Different outcome (assessed histological parameter)

Table S2. Excluded Studies and Reasons for Exclusion. (continued)

Citations	Reasons
Rafal ES, Griffiths CE, Ditre CM, Finkel LJ, Hamilton TA, Ellis CN, Voorhees JJ. Topical tretinoin (retinoic acid) treatment for liver spots associated with photodamage. <i>N Engl J Med.</i> 1992 Feb 6;326(6):368-74. doi: 10.1056/NEJM199202063260603. PMID: 1729619.	Different outcome (assessed liver spots)
Ho ET, Trookman NS, Sperber BR, Rizer RL, Spindler R, Sonti S, Gotz V, Mehta R. A randomized, double-blind, controlled comparative trial of the anti-aging properties of non-prescription tri-retinol 1.1% vs. prescription tretinoin 0.025%. <i>J Drugs Dermatol.</i> 2012 Jan;11(1):64-9. PMID: 22206079.	Not a vehicle-controlled trial
Bagatin E, Gonçalves HS, Sato M, Almeida LMC, Miot HA. Comparable efficacy of adapalene 0.3% gel and tretinoin 0.05% cream as treatment for cutaneous photoaging. <i>Eur J Dermatol.</i> 2018 Jun 1;28(3):343-350. doi: 10.1684/ejd.2018.3320. PMID: 30105991.	Not a vehicle-controlled trial
Chien AL, Kim DJ, Cheng N, Shin J, Leung SG, Nelson AM, Zang J, Suh H, Rainer B, Wallis L, Okoye GA, Loss M, Kang S. Biomarkers of Tretinoin Precursors and Tretinoin Efficacy in Patients With Moderate to Severe Facial Photodamage: A Randomized Clinical Trial. <i>JAMA Dermatol.</i> 2022 Aug 1;158(8):879-886. doi: 10.1001/jamadermatol.2022.1891. PMID: 35675051; PMCID: PMC9178500.	Not a vehicle-controlled trial
Bagatin E, Guadanhim LR, Enokihara MM, Sanudo A, Talarico S, Miot HA, Gibson L. Low-dose oral isotretinoin versus topical retinoic acid for photoaging: a randomized, comparative study. <i>Int J Dermatol.</i> 2014 Jan;53(1):114-22. doi: 10.1111/ijd.12191. Epub 2013 Oct 29. PMID: 24168514.	Not a vehicle-controlled trial
Kligman DE, Draelos ZD. Combination Superficial Peels With Salicylic Acid and Post-Peel Retinoids. <i>J Drugs Dermatol.</i> 2016 Apr;15(4):442-50. PMID: 27050699.	Not a vehicle-controlled trial
Miura T, Takada A, Ooe M. Tretinoin cyclodextrin complex (RA/CyD) causes less irritation with an equal antiwrinkle effect compared with conventional tretinoin: clinical and histologic studies of photoaged skin. <i>Aesthetic Plast Surg.</i> 2012 Aug;36(4):971-81. doi: 10.1007/s00266-012-9903-4. Epub 2012 Apr 27. PMID: 22538278.	Not a vehicle-controlled trial
Sumita JM, Miot HA, Soares JLM, Raminelli ACP, Pereira SM, Ogawa MM, Picosse FR, Guadanhim LRS, Enokihara MMSS, Leonardi GR, Bagatin E. Tretinoin (0.05% cream vs. 5% peel) for photoaging and field cancerization of the forearms: randomized, evaluator-blinded, clinical trial. <i>J Eur Acad Dermatol Venereol.</i> 2018 Oct;32(10):1819-1826. doi: 10.1111/jdv.15020. Epub 2018 May 27. PMID: 29704456.	Not a vehicle-controlled trial
Leyden JJ, Grove GL, Grove MJ, Thorne EG, Lufrano L. Treatment of photodamaged facial skin with topical tretinoin. <i>J Am Acad Dermatol.</i> 1989 Sep;21(3 Pt 2):638-44. doi: 10.1016/s0190-9622(89)70231-0. PMID: 2674225.	Different outcome scale (lack data on wrinkle improvement percentages)
Olsen EA, Katz HI, Levine N, Nigra TP, Pochi PE, Savin RC, Shupack J, Weinstein GD, Lufrano L, Jou HC. Sustained improvement in photodamaged skin with reduced tretinoin emollient cream treatment regimen: effect of once-weekly and three-times-weekly applications. <i>J Am Acad Dermatol.</i> 1997 Aug;37(2 Pt 1):227-30. doi: 10.1016/s0190-9622(97)80129-6. PMID: 9270508.	Different outcome scale (lack data on wrinkle improvement percentages)
Samuel M, Brooke RC, Hollis S, Griffiths CE. Interventions for photodamaged skin. <i>Cochrane Database Syst Rev.</i> 2005 Jan 25;(1):CD001782. doi: 10.1002/14651858.CD001782.pub2. Update in: <i>Cochrane Database Syst Rev.</i> 2015;6:CD001782. PMID: 15674885.	Not a randomized trial

Table S3. Clinical Improvement and Patient Assessment of all Studies Included in Meta-Analysis.

Study	Fine Wrinkles Clinical Improvement Rates (Patient number/Total patient)				Coarse Wrinkles Clinical Improvement Rates (Patient number/Total patient)				Overall self-assessment of global response (% of subjects)			
	Grades of Clinical Improvement (% for Quantification)	Tretinoin-treated	Vehicle-treated	Grades of Clinical Improvement (% for Quantification)	Tretinoin-treated	Vehicle-treated	Grades of Clinical Improvement (% for Quantification)	Tretinoin-treated	Vehicle-treated	Grades of Clinical Improvement (% for Quantification)	Tretinoin-treated	Vehicle-treated
Weiss et al, 1988	Tretinoin 0.1% Much improved Improved Slightly improved No change or worse	0/15 1/15 13/15 1/15	0/0 0/0 0/0 15/15	Much improved Improved Slightly improved No change or worse	0/0 0/0 6/15 9/15	0/0 0/0 0/0 15/15	ND <sup>y</sup>	0/0 0/0 6/15 9/15	0/0 0/0 0/0 15/15	ND <sup>y</sup>	ND	ND
Weinstein et al, 1991	Tretinoin 0.05% Tretinoin 0.01%	60/85 <sup>#</sup> 51/84 <sup>#</sup>	31/82 <sup>#</sup>	ND <sup>y</sup>	ND	ND	ND <sup>y</sup>	ND	ND	(Tretinoin doses) Overall improvement (includes much improved and somewhat improved)	0.05%; 0.01% 87; 71	43
Olsen et al, 1992	Tretinoin 0.05% Tretinoin 0.01% Tretinoin 0.01% ND <sup>y</sup>	43/76 <sup>#</sup> 29/73 <sup>#</sup> 20/75 <sup>#</sup>	27/72 <sup>#</sup>	ND <sup>y</sup>	ND	ND	ND <sup>y</sup>	ND	ND	(Tretinoin doses) Improved • Much improved • Somewhat improved	0.05%; 0.01%; 0.001% 78; 70; 60 14; 10; 9 63; 60; 51	61 7 54
Andreano et al, 1993	Tretinoin 0.01% Much improved Improved Slightly Improved No improvement/worse	0/17 3/17 10/17 4/17	0/17 0/17 3/17 14/17	Much improved Improved Slightly Improved No improvement/worse	0/17 1/17 6/17 10/17	1/17 0/17 0/17 16/17	ND <sup>y</sup>	0/17 1/17 6/17 10/17	1/17 0/17 0/17 16/17	ND <sup>y</sup>	76	47
Lowe et al, 1994	Tretinoin 0.05% ND <sup>y</sup>	45/62	26/63	ND <sup>y</sup>	32/62	22/63	ND <sup>y</sup>	32/62	22/63	ND <sup>y</sup>	60	32
Niyady et al, 2001	Tretinoin 0.02% ND <sup>y</sup>	Study1: 50/77 <sup>#</sup> Study2: 46/82 <sup>#</sup>	Study1: 30/83 <sup>#</sup> Study2: 34/86 <sup>#</sup>	ND <sup>y</sup>	Study1: 33/77 <sup>#</sup> Study2: 31/82 <sup>#</sup>	Study1: 20/83 <sup>#</sup> Study2: 18/86 <sup>#</sup>	Improved • Much improved • Somewhat improved	Study1: 33/77 <sup>#</sup> Study2: 31/82 <sup>#</sup>	Study1: 20/83 <sup>#</sup> Study2: 18/86 <sup>#</sup>	Improved • Much improved • Somewhat improved	Study1; Study2 83; 83 25; 29 58; 54	Study 1; Study 2 64; 72 7; 24 57; 48
Kang et al, 2005	Tretinoin 0.05% ND <sup>y</sup>	76/101 <sup>#</sup>	56/103 <sup>#</sup>	ND <sup>y</sup>	44/101 <sup>#</sup>	38/103 <sup>#</sup>	ND <sup>y</sup>	44/101 <sup>#</sup>	38/103 <sup>#</sup>	ND <sup>y</sup>	ND	ND
Weiss et al, 2006	Tretinoin 0.1% ND <sup>y</sup>	16/18 <sup>#</sup>	5/22 <sup>#</sup>	ND <sup>y</sup>	3/18 <sup>#</sup>	1/22 <sup>#</sup>	ND <sup>y</sup>	3/18 <sup>#</sup>	1/22 <sup>#</sup>	ND <sup>y</sup>	65	35

ND, no data. <sup>y</sup>Results of clinical improvement without adequate definition. <sup>#</sup>Patient numbers are from estimated calculation from provided data.

**Table S4. Summary of the Topical Retinoid Interventions Administered in the Study Treatment Arms of the Retrieved Trials.**

First author & year	Photoaging severity at baseline	Duration	Topical retinoid product / manufacturer	Daily topical retinoid frequency (per-protocol N)	Control (per-protocol N)	Wrinkle improvement measurement	AE associated with topical retinoid treatment
Weiss 1988	mild to moderate	16 weeks	Tretinoin 0.1% cream (Retin-A, Ortho Pharmaceutical Corp, Raritan, NJ)	Once nightly (15)	Matching vehicle (15)	0-4 points scale converted to improvement scores <sup>1</sup>	Most common AE was dermatitis experienced by 92% of patients using tretinoin and no AE seen in vehicle group
Weinstein 1991	mild or moderate	24 weeks	Tretinoin 0.05% or 0.01% emollient cream (Renova)	Once daily (169)	Matching vehicle (82)	0-9 point scale converted to percentage of subjects' improvement	Most common AE were peeling and dryness and were highest in Tretinoin 0.05% (64%) compared with vehicle (25%)
Olsen 1992	mild or moderate	24 weeks	Tretinoin 0.05% Tretinoin 0.01% Tretinoin 0.001% emollient cream (Renova)	Once every evening (76)	Comparable vehicle (72)	10 point scale converted to percentage of subjects' improvement	Most common AE was dryness and was highest in Tretinoin 0.05% (65%) compared with vehicle (33%)
Andreano 1993	mild or moderate	48 weeks (24 weeks <sup>2</sup> )	Tretinoin 0.01% emollient cream (RW Johnson Pharmaceutical Research Institute, Raritan, NJ)	Daily (17)	Matching vehicle (17)	0-9 points scale converted to improvement scores <sup>1</sup>	AE rate was similar between the tretinoin (82%) and the vehicle (76%) group. Most common AE were dryness, peeling, and acne.
Lowe 1994	mild-to-moderate	24 weeks	Tretinoin 0.05% (Janssen-Cilag (Australia) Pty Ltd)	Once nightly (62)	Matching vehicle (63)	0-6 points scale converted to percentage of subjects' improvement	49% of the tretinoin treatment group experienced AE compared to 35% in the vehicle group. Most common AE was irritation.

**Table S4. Summary of the Topical Retinoid Interventions Administered in the Study Treatment Arms of the Retrieved Trials. (continued)**

First author & year	Photoaging severity at baseline	Duration	Topical retinoid product / manufacturer	Daily topical retinoid frequency (per-protocol N)	Control (per-protocol N)	Wrinkle improvement measurement	AE associated with topical retinoid treatment
Nyrady 2001	moderate-to-severe	24 weeks	Tretinoin 0.02% cream	Once nightly (Study 1: 77 Study 2: 82)	Matching vehicle (Study 1: 83 Study 2: 86)	0-9 point scale converted to percentage of subjects' improvement	Most common AE was irritation occurred in 20% (study 1) and 38% (study 2) of the treatment group.
Kang 2005	moderate-to-severe	2 years (24 months <sup>2</sup> )	Tretinoin 0.05% emollient cream	Once nightly (101)	Matching vehicle (103)	10 point scale converted to percentage of subjects' improvement	AE rate was similar between the tretinoin (83%) and the vehicle (82%) group. Most common AE were irritation and upper respiratory tract infection
Weiss 2006	moderate-to-severe	6 months double-blinded period <sup>2</sup>	Tretinoin 0.1% Microsphere gel	Once nightly (22)	Matching vehicle (23)	10 point scale converted to percentage of subjects' improvement	AE rate was similar between the tretinoin (32%) and the vehicle (30%) group. Most common AE was infection

AE, adverse effect. <sup>1</sup>Improvement scores were calculated into percentage by combining all the patients with “slightly improved”, “improved”, and “much improved” groups and divided by the total participants. <sup>2</sup>Primary outcome of wrinkle improvement was extracted by this end-point of the trial.

**Table S5 Detailed Quality Assessment of the Included Studies using the Cochrane Risk of Bias Tool (Version 2)**

First Author	Randomization process	Intervention adherence	Missing outcome data	Outcome measurement	Selective reporting	Overall RoB
Weiss 1988	L	L	L	L	L	L
Weinstein 1991	L	L	L	L	S <sup>1</sup>	S
Olsen 1992	L	L	L	L	S <sup>2</sup>	S
Andreano 1993	L	L	L	L	L	L
Lowe 1994	L	L	L	L	L	L
Nyrady 2001	L	L	L	L	L	L
Kang 2005	L	L	L	L	L	L
Weiss 2006	L	L	L	L	L	L

H, high risk of bias; L, low risk of bias; RoB, risk of bias; S, some risk of bias. <sup>1</sup>This study did not provide data on tretinoin's treatment effect on coarse wrinkling. <sup>2</sup>This study only provided p-values of one of the three concentrations of tretinoin being tested.