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A Comprehensive Systematic Review of Treatment Strategies for Keloid and Hypertrophic Scar

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ABSTRACT

Introduction: Keloid and hypertrophic scars represent a significant clinical challenge due to their complex pathogenesis, propensity for recurrence, and psychosocial impact on patients. Despite numerous available interventions, there is no universally accepted gold-standard treatment, and evidence on comparative efficacy and safety remains fragmented.

Methods: A systematic evidence synthesis was conducted based on a comprehensive screening of 80 studies, including randomized controlled trials, systematic reviews, and meta-analyses. Studies were selected based on predefined criteria including clinically diagnosed scars, therapeutic interventions, human studies, and quantitative outcome reporting. Data were extracted on treatment strategies, scar characteristics, patient demographics, effectiveness, safety, and study design.

Results: Combination therapies consistently outperformed monotherapies. Triamcinolone acetonide (TAC) combined with 5-fluorouracil (5-FU) showed superior efficacy (77.2–93.3% response) and lower recurrence compared to TAC alone (Liu et al., 2020; Khalid et al., 2019). TAC with botulinum toxin A also ranked highly (SUCRA 82.2%) (Yang et al., 2021). Verapamil demonstrated a better safety profile but slower onset of action. Laser therapies, especially fractional CO_2 with 5-FU, showed significant scar improvement (Foppiani et al., 2024). Surgical excision with adjuvant high-dose-rate brachytherapy yielded the lowest recurrence (3.1%) (van Leeuwen et al., 2014).

Discussion: The synthesis highlights the importance of multimodal, context-specific treatment strategies. Combination regimens address multiple pathological pathways, enhancing outcomes while mitigating adverse effects. Discrepancies in monotherapy efficacy are attributed to variations in protocols, concentrations, and scar characteristics.

Conclusion: Combination therapy, particularly TAC+5-FU, represents the most effective and balanced approach for most keloid and hypertrophic scar cases. Treatment should be individualized based on scar type, location, size, patient skin type, and tolerance to side effects. Future research should focus on standardized protocols, long-term follow-up, and novel targeted therapies.

Keywords: Keloid, hypertrophic scar, triamcinolone acetonide, 5-fluorouracil, combination therapy, laser therapy, systematic review, meta-analysis.

INTRODUCTION

Background: Keloid and hypertrophic scars are abnormal fibrous proliferations that result from an aberrant wound healing process, characterized by excessive collagen deposition and persistent inflammation (Worley et al., 2023). These scars extend beyond the original wound boundaries and often cause pruritus, pain, cosmetic disfigurement, and significant psychological distress (Walsh et al., 2023). The pathophysiology involves complex interactions between fibroblasts, inflammatory cytokines, growth factors, and genetic predispositions, making treatment challenging and recurrence common.

Research Objectives: This comprehensive evidence synthesis aims to:

1. Systematically review and compare the efficacy and safety of current treatment modalities for keloid and hypertrophic scars.
2. Evaluate the role of monotherapy versus combination therapy.
3. Identify optimal treatment strategies based on scar characteristics and patient demographics.
4. Provide evidence-based recommendations for clinical practice.

Research Benefits: This review consolidates high-level evidence from 80 studies to guide clinicians in making informed, individualized treatment decisions. It clarifies conflicting data, highlights superior therapeutic combinations, and underscores the importance of safety profiles, thereby improving patient outcomes and satisfaction.

Hypothesis: It is hypothesized that combination therapies targeting multiple pathogenic pathways will demonstrate superior efficacy and lower recurrence rates compared to monotherapies. Furthermore, tailored treatment approaches based on scar type, location, and patient factors will yield optimal clinical results.

Research Gap: Despite numerous studies, inconsistencies exist regarding the superiority of specific monotherapies (e.g., TAC vs. 5-FU), and long-term recurrence data for many newer modalities remain limited (King et al., 2024). There is also a lack of consensus on standardized treatment protocols, optimal dosing, and sequencing of multimodal therapies.

Novelty: This synthesis provides an updated, extensive comparison of both established and emerging therapies, including network meta-analyses ranking treatment efficacy. It uniquely integrates data on novel agents (e.g., vitamin D, platelet-rich plasma, bleomycin) and emphasizes context-specific treatment algorithms, reconciling apparent contradictions in the literature through detailed analysis of study methodologies and treatment contexts.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the treatment strategies for keloid and hypertrophic scar.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population**: Does the study include participants with clinically diagnosed keloid scars and/or hypertrophic scars?
- **Intervention**: Does the study evaluate a therapeutic intervention for treating keloid or hypertrophic scars?

- **Study Design**: Is the study a randomized controlled trial, controlled clinical trial, or systematic review/meta-analysis?
- **Outcomes**: Does the study report quantitative outcomes related to scar improvement (e.g., scar size, appearance, symptoms, or validated scar assessment scales)?
- **Study Population Type**: Is this a human study (not exclusively in vitro or animal studies)?
- **Treatment Focus**: Does the study focus on treatment of existing keloid or hypertrophic scars (rather than prevention in unaffected individuals or normal wound healing)?
- **Study Quality and Size**: Is the study NOT a case report, case series with fewer than 10 participants, conference abstract, editorial, letter, or opinion piece?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Keloid scar	Treatment strategy	Monotherapy	Scar improvement
Keyword 2	Hypertrophic scar	Therapeutic intervention	Combination therapy	Treatment efficacy
Keyword 3	Abnormal scar	Management approach	Standard treatment	Recurrence rate
Keyword 4	Pathological scar	Clinical therapy	Alternative therapy	Patient satisfaction

The Boolean MeSH keywords inputted on databases for this research are: *("Keloid scar" OR "Hypertrophic scar" OR "Abnormal scar" OR "Pathological scar") AND ("Treatment strategy" OR*

"Therapeutic intervention" OR "Management approach" OR "Clinical therapy") AND ("Monotherapy" OR "Combination therapy" OR "Standard treatment" OR "Alternative therapy") AND ("Scar improvement" OR "Treatment efficacy" OR "Recurrence rate" OR "Patient satisfaction")

Data extraction

- **Treatment Strategy**:

  Extract comprehensive details about the specific treatment strategy used for keloid and hypertrophic scars, including:

  - Type of treatment (intralesional injection, topical therapy, laser therapy, surgical excision, physical therapy, regenerative medicine, etc.)
  - Specific agent/device used (e.g., triamcinolone acetonide, 5-fluorouracil, pulsed-dye laser, silicone gel)
  - Dosage/concentration (e.g., 20 mg/mL TAC, 50 mg/mL 5-FU)
  - Treatment protocol (frequency, duration, number of sessions)
  - Delivery method and technique details
  - Whether used as monotherapy or combination therapy
  - If combination therapy, specify all components and their proportions

- **Scar Characteristics**:

  Extract characteristics of the keloid and hypertrophic scars being treated that may influence treatment response, including:

  - Scar type (keloid vs. hypertrophic)
  - Scar location/anatomical site
  - Scar age/maturity (time since formation)
  - Scar size, height, and volume measurements

- Cause of original injury (surgical, traumatic, burn, etc.)
- Previous treatment history
- Baseline scar assessment scores (Vancouver Scar Scale, POSAS, etc.)
- Any scar-specific features mentioned (vascularity, pigmentation, texture)

- **Patient Demographics**:

  Extract patient characteristics relevant to keloid and hypertrophic scar treatment response, including:

  - Age and age range
  - Gender distribution
  - Ethnicity/race (particularly Fitzpatrick skin type for laser treatments)
  - Sample size
  - Comorbidities that may affect healing
  - Previous scar treatment history
  - Any patient-specific factors mentioned as influencing treatment outcomes

- **Effectiveness Results**:

  Extract all measures of treatment effectiveness for keloid and hypertrophic scars, including:

  - Primary outcome measures used (scar assessment scales, objective measurements)
  - Percentage improvement or reduction in scar parameters
  - Before and after measurements with statistical significance
  - Response rates (complete response, partial response, no response)
  - Time to improvement and duration of follow-up
  - Recurrence rates for surgical treatments
  - Patient satisfaction scores
  - Quality of life improvements

- Functional improvements (range of motion, etc.)
- Any standardized scar assessment tool results (POSAS, VSS, MSS)

- **Safety Profile**:

  Extract safety and tolerability data specific to keloid and hypertrophic scar treatments, including:

  - Incidence and type of adverse events
  - Severity of side effects (mild, moderate, severe)
  - Treatment-related complications (skin atrophy, hypopigmentation, telangiectasia, pain, infection)
  - Discontinuation rates due to adverse effects
  - Long-term safety concerns
  - Contraindications identified
  - Any treatment-specific safety considerations mentioned
  - Patient tolerance and acceptability of treatment

- **Study Design**:

  Extract methodological details affecting the reliability of evidence for keloid and hypertrophic scar treatment, including:

  - Study design (RCT, cohort, case series, systematic review, meta-analysis)
  - Randomization and blinding methods
  - Control group details (placebo, active comparator, no treatment)
  - Study duration and follow-up period
  - Sample size and power calculations
  - Inclusion and exclusion criteria specific to scar types
  - Assessment methods for outcome measures

- Risk of bias considerations
- Study limitations acknowledged by authors

- **Comparative Findings**:

  When multiple treatment strategies for keloid and hypertrophic scars are compared, extract:

  - Direct head-to-head comparison results with statistical significance
  - Ranking or hierarchy of treatment effectiveness
  - Superiority or inferiority claims between treatments
  - Subgroup analyses showing differential effects by scar type, patient characteristics, or other factors
  - Network meta-analysis results if available
  - Authors' recommendations for treatment selection
  - Cost-effectiveness comparisons if provided
  - Factors influencing choice between treatment options

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Keloid scar") AND ("Treatment strategy") AND ("Scar improvement" OR "Treatment efficacy" OR "Recurrence rate" OR "Patient satisfaction")*	2
Semantic Scholar	*("Keloid scar" OR "Hypertrophic scar" OR "Abnormal scar" OR "Pathological scar") AND ("Treatment strategy" OR "Therapeutic intervention" OR "Management approach" OR "Clinical therapy") AND ("Monotherapy" OR "Combination therapy" OR "Standard treatment" OR "Alternative therapy") AND ("Scar improvement" OR "Treatment efficacy" OR "Recurrence rate" OR "Patient satisfaction")*	252
Springer	*("Keloid scar" OR "Hypertrophic scar" OR "Abnormal scar" OR "Pathological scar") AND ("Treatment strategy" OR "Therapeutic intervention" OR "Management approach" OR "Clinical therapy") AND ("Monotherapy" OR "Combination therapy" OR "Standard treatment" OR "Alternative therapy") AND ("Scar improvement" OR "Treatment efficacy" OR "Recurrence rate" OR "Patient satisfaction")*	69
Google Scholar	*("Keloid scar" OR "Hypertrophic scar" OR "Abnormal scar" OR "Pathological scar") AND ("Treatment strategy" OR "Therapeutic intervention" OR "Management approach" OR "Clinical therapy") AND ("Monotherapy" OR "Combination therapy" OR "Standard treatment" OR "Alternative therapy") AND ("Scar improvement" OR "Treatment efficacy" OR "Recurrence rate" OR "Patient satisfaction")*	344
Wiley Online Library	*("Keloid scar" OR "Hypertrophic scar" OR "Abnormal scar" OR "Pathological scar") AND ("Treatment strategy" OR "Therapeutic intervention" OR "Management approach" OR "Clinical therapy") AND ("Monotherapy" OR "Combination therapy" OR "Standard treatment" OR "Alternative therapy") AND ("Scar improvement" OR "Treatment efficacy" OR "Recurrence rate" OR "Patient satisfaction")*	95

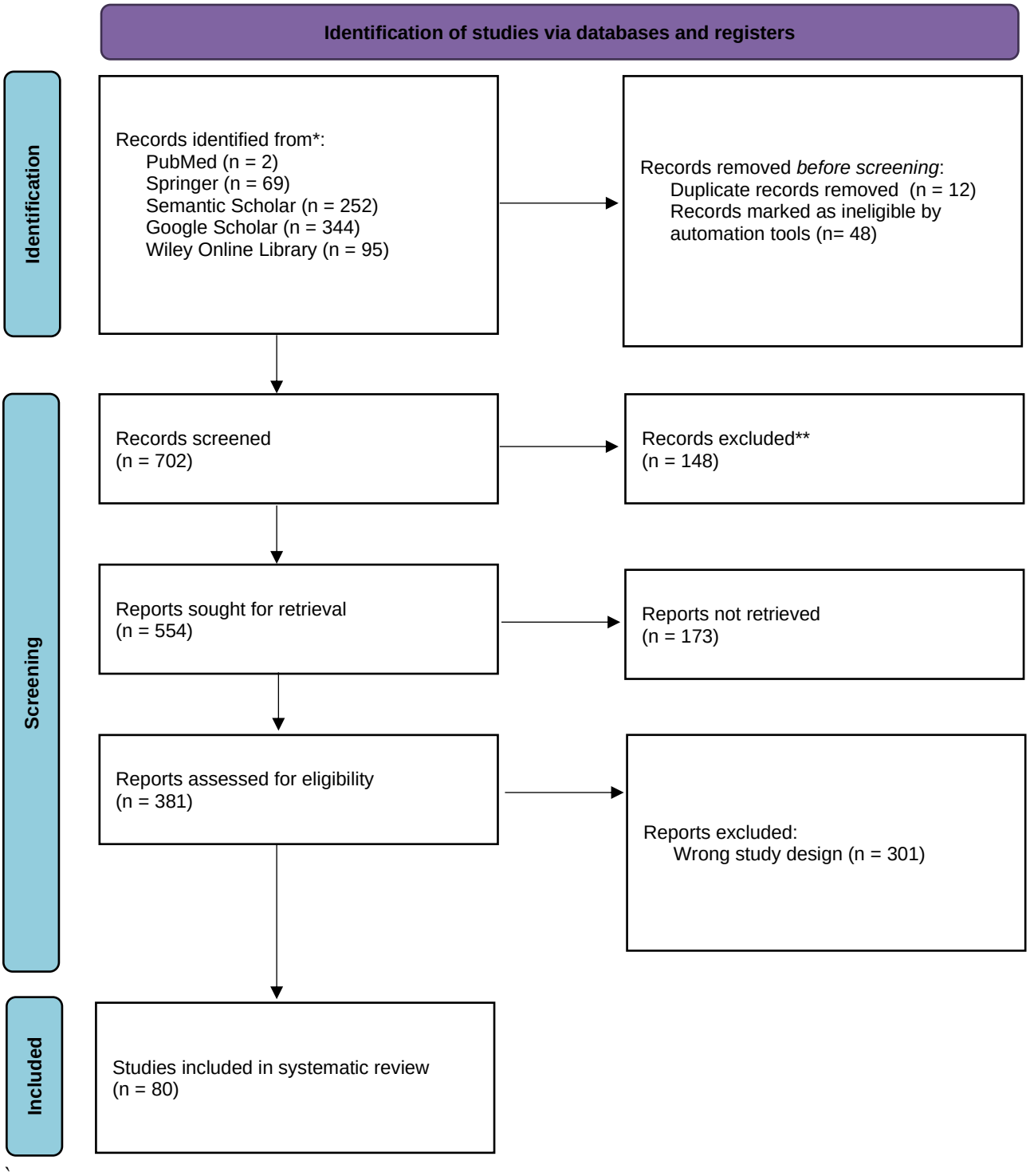

Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	**Bias related to temporal precedence** Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)?	**Bias related to selection and allocation** Was there a control group?	**Bias related to confounding factors** Were participants included in any comparisons similar?	**Bias related to administration of intervention/exposure** Were the participants included in any comparisons receiving similar treatment/ care, other than the exposure or intervention of interest?	**Were there multiple measurements of the outcome, both pre and post the intervention/exposure?**	**Were the outcomes of participants included in any comparisons measured in the same way?**	**Were outcomes measured in a reliable way?**	**Bias related to participant retention** Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	**Statistical conclusion validity** Was appropriate statistical analysis used?
Minglei Bi et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Zhihao Zhuang et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Hietanen et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓

M. Dirr et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Kierra Jackson et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
B. Worley et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
F. A. Khalid et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. A. Khan et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Ellis et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Srivastava et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sunil Srivastava et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Y. M. Neinaa et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Alexandra F. Chandra et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
I-Chang Lai et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ripala Acharya et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓

B. Shah et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Shah et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
Siqi Fu et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Foppiani et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ru Wang et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Srivastava et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. S. Hewedy et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Mavilakandy et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Wei Zhang et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. V. van Leeuwen et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
Niti Tawaranurak et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Zhengying Jiang et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓

B. Behera et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Comparison of TAC vs. TAC+5-FU, 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Li-Tsang et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yazhuo Li et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Elshymaa E Raslan et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Aliyah King et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
F. A. Khalid et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Peixuan Zhang et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. S. K. Menon et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Prabhu et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
Junxian Wen et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓

Shen Hou et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Christophe Abi Zeid Daou et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Zouboulis et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Asma Batool et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Abedini et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Zabihollah Shahmoradi et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sara AbdAlbaset et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. A. Rahman et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ruiquan Liu et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jing Kuang et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yiqiu Zhang et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓

Mohamed M. Khedr et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Aman Goyal et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Qiu-Yun Xu et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
X. J. Liu et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Pu Wang et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Aman Goyal et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sadia Abbasi et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Lin et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Bassel Younes et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
B. Nedelec et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jianzhen Shi et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yasir T. Radhi et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓

Yan-Wei Sun et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sha Yang et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Douglas D. Leventhal et al., 2006	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yawei Bao et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Breno de Amaral Gandini et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
W. Manuskiatti et al., 2002	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Asilian et al., 2006	✓	✓	✓	✗	✓	✗	✓	✓	✓
Alireza Jafarzadeh et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Laura A. Walsh et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Nischwitz et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Choi et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Keshvad Hedayatyanfard et	✓	✓	✓	✗	✓	✗	✓	✓	✓

al., 2018									
A. Sadeghinia et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Oosterhoff et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. V. van Leeuwen et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Zhengying Jiang et al., 2020a	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jonathan S. Friedstat et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yiming Ren et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Koorosh Ahmadpour et al., 2006	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

The evidence base for keloid and hypertrophic scar treatment comprises diverse study designs across 80 sources. The following table summarizes key characteristics of the included literature.

Study	Scar Type	Primary Treatments Evaluated
Minglei Bi et al., 2019	Keloid and hypertrophic	Botulinum toxin type A vs. corticosteroid
Zhihao Zhuang et al., 2020	Keloid and hypertrophic	TAC, 5-FU, verapamil, botulinum toxin
K. Hietanen et al., 2019	Keloid	TAC vs. 5-FU
M. Dirr et al., 2022	Keloid and hypertrophic	Intralesional injection, laser therapy
Kierra Jackson et al., 2025	Keloid and hypertrophic	PGT, triamcinolone, verapamil, laser
B. Worley et al., 2023	Keloid and hypertrophic	Intralesional, physical, topical, laser
F. A. Khalid et al., 2019	Keloid and hypertrophic	TAC vs. TAC+5-FU
M. A. Khan et al., 2014	Keloid and hypertrophic	TAC vs. TAC+5-FU
M. Ellis et al., 2020	Keloid	Surgery + adjuvant therapies
S. Srivastava et al., 2018	Keloid	TAC, 5-FU, TAC+5-FU

Study	Scar Type	Primary Treatments Evaluated
Sunil Srivastava et al., 2017	Keloid	TAC, 5-FU, TAC+5-FU
Y. M. Neinaa et al., 2021	Keloid	BTX-A, PRP, TAC
Alexandra F. Chandra et al., 2025	Keloid	TAC combinations with 5-FU, PDL, bleomycin
I-Chang Lai et al., 2025	Keloid and hypertrophic	Multiple intralesional agents
Ripala Acharya et al., 2024	Keloid and hypertrophic	TAC vs. TAC+5-FU
B. Shah et al., 2024	Keloid and hypertrophic	TAC vs. 5-FU
M. Shah et al., 2014	Keloid	5-FU, CO2 laser, TAC
Siqi Fu et al., 2023	Keloid	Surgery + radiotherapy vs. laser + steroids
J. Foppiani et al., 2024	Keloid and hypertrophic	FCO2 + 5-FU
Ru Wang et al., 2021	Keloid	Corticosteroid injection vs. radiotherapy
S. Srivastava et al., 2019	Keloid	CO2 laser, TAC, verapamil
E. S. Hewedy et al., 2020	Keloid	TAC vs. TAC+PRP
A. Mavilakandy et al., 2023	Keloid and hypertrophic	TAC+5-FU vs. monotherapy

Study	Scar Type	Primary Treatments Evaluated
Wei Zhang et al., 2022	Keloid and hypertrophic	Verapamil vs. TAC
M. V. van Leeuwen et al., 2014	Keloid	Excision + HDR brachytherapy
Niti Tawaranurak et al., 2022	Keloid	FCO2 + topical TA vs. intralesional TA
Zhengying Jiang et al., 2020	Keloid and hypertrophic	Verapamil vs. TAC
B. Behera et al., 2016	Keloid	ILTA + CO2 laser vs. ILTA + cryotherapy
Comparison of TAC vs. TAC+5-FU, 2022	Keloid	TAC vs. TAC+5-FU
C. Li-Tsang et al., 2010	Hypertrophic	Pressure therapy, silicone gel, combination
Yazhuo Li et al., 2022	Keloid	Excision + 5-FU/betamethasone vs. radiotherapy
Elshymaa E Raslan et al., 2024	Hypertrophic	Botulinum toxin type A
Aliyah King et al., 2024	Keloid	5-FU monotherapy
F. A. Khalid et al., 2018	Keloid	Excision + 5-FU/TAC vs. excision + radiotherapy

Study	Scar Type	Primary Treatments Evaluated
Peixuan Zhang et al., 2023	Hypertrophic	Pressure + silicone vs. pressure alone
T. S. K. Menon et al., 2025	Keloid	Triple combination vs. TAC alone
A. Prabhu et al., 2012	Keloid	5-FU vs. TAC
Junxian Wen et al., 2024	Keloid	DWL + betamethasone
Shen Hou et al., 2023	Keloid	Punch excision + steroid injection
Christophe Abi Zeid Daou et al., 2025	Keloid and hypertrophic	FCO2 laser monotherapy
C. Zouboulis et al., 2020	Keloid	Cryosurgery ± intralesional corticosteroids
Asma Batool et al., 2025	Keloid	Verapamil vs. TAC
R. Abedini et al., 2018	Keloid and hypertrophic	Verapamil vs. TAC
Zabihollah Shahmoradi et al., 2024	Keloid	TAC + bevacizumab vs. TAC alone
Sara AbdAlbaset et al., 2025	Keloid	TAC vs. TAC+5-FU
S. A. Rahman et al., 2020	Hypertrophic	Nd:YAG laser ± steroid/BTA
Ruiquan Liu et al., 2020	Keloid and hypertrophic	Verapamil vs. TAC

Study	Scar Type	Primary Treatments Evaluated
Jing Kuang et al., 2021	Keloid and hypertrophic	Verapamil vs. triamcinolone
Yiqiu Zhang et al., 2023	Hypertrophic	CO2 laser + IPL vs. IPL alone
Mohamed M. Khedr et al., 2019	Hypertrophic	Nd:YAG laser vs. E-light
Aman Goyal et al., 2024	Keloid	Vitamin D vs. TAC
Qiu-Yun Xu et al., 2023	Keloid and hypertrophic	Intralesional TAC
X. J. Liu et al., 2020	Keloid	TAC vs. TAC+5-FU
Pu Wang et al., 2020	Keloid and hypertrophic	Verapamil vs. TAC
Aman Goyal et al., 2023	Keloid	Vitamin D vs. TAC
Sadia Abbasi et al., 2025	Keloid	TAC + cryotherapy vs. TAC alone
N. Lin et al., 2021	Keloid	5-FU at different concentrations + TAC
Bassel Younes et al., 2025	Hypertrophic	FCO2 ± 5-FU or TAC
B. Nedelec et al., 2020	Hypertrophic	Corticosteroid injection
Jianzhen Shi et al., 2024	Keloid and hypertrophic	TAC + BTA
Yasir T. Radhi et al., 2025	Keloid	Debulking + TAC vs. debulking alone
Yan-Wei Sun et al., 2016	Keloid	Low-dose 5-FU + TAC vs. TAC

Study	Scar Type	Primary Treatments Evaluated
Sha Yang et al., 2021	Keloid and hypertrophic	Multiple intralesional and topical agents
Douglas D. Leventhal et al., 2006	Keloid and hypertrophic	Multiple treatment modalities
Yawei Bao et al., 2019	Keloid and hypertrophic	TAC, 5-FU, verapamil, combinations
Breno de Amaral Gandini et al., 2025	Keloid and hypertrophic	Non-surgical modalities
W. Manuskiatti et al., 2002	Keloid and hypertrophic	TAC, 5-FU, PDL
A. Asilian et al., 2006	Keloid and hypertrophic	TAC, TAC+5-FU, TAC+5-FU+PDL
Alireza Jafarzadeh et al., 2023	Keloid and hypertrophic	PRP, SVF, stem cell-conditioned medium
Laura A. Walsh et al., 2023	Keloid	Multiple modalities
S. Nischwitz et al., 2020	Hypertrophic	TAC+5-FU, pressure, silicone
C. Choi et al., 2022	Hypertrophic	Silicone, TAC, laser
Keshvad Hedayatyanfard et al., 2018	Keloid and hypertrophic	Losartan ointment
A. Sadeghinia et al., 2012	Keloid	TAC vs. 5-FU tattooing
T. Oosterhoff et al., 2020	Keloid and hypertrophic	Laser therapy

Study	Scar Type	Primary Treatments Evaluated
M. V. van Leeuwen et al., 2015	Keloid	Surgery + adjuvant irradiation
Zhengying Jiang et al., 2020a	Keloid and hypertrophic	TAC vs. TAC+5-FU
Jonathan S. Friedstat et al., 2014	Hypertrophic (burn)	Multiple modalities
Yiming Ren et al., 2017	Keloid and hypertrophic	TAC vs. TAC+5-FU
Koorosh Ahmadpour et al., 2006	Keloid and hypertrophic	Bleomycin tattoo vs. cryotherapy + TAC

Sample sizes ranged from 10 patients to over 5,500 keloids. Follow-up periods varied substantially, from 6 weeks to 10 years in some prospective studies.

Effects of Treatment Modalities

Intralesional Corticosteroid Monotherapy

Triamcinolone acetonide (TAC) remains the most widely evaluated intralesional agent for keloid and hypertrophic scars. Standard concentrations range from 10 mg/mL to 40 mg/mL, with treatment protocols typically involving injections at 2-4 week intervals.

Study	TAC Concentration	Treatment Outcome	Statistical Significance
K. Hietanen et al., 2019	20 mg/mL	60% remission rate at 6 months	No significant difference vs. 5-FU

Study	TAC Concentration	Treatment Outcome	Statistical Significance
R. Abedini et al., 2018	40 mg/mL	Mean zero VSS scores achieved by week 15	Superior to verapamil
B. Nedelec et al., 2020	10 mg/mL	Significant decrease in thickness and increase in pliability	p=0.0003 vs. control
Kierra Jackson et al., 2025	Not specified	82.2% scar reduction	Most effective among evaluated treatments
Asma Batool et al., 2025	40 mg	58.28% reduction in Vancouver score	Superior to verapamil (p<0.001)

TAC demonstrates consistent efficacy in reducing scar height, vascularity, and improving pliability. However, response rates vary considerably, with some studies reporting remission rates of 60% while others suggest approximately 50% of keloids may be steroid-resistant. The systematic review by Kierra Jackson et al. ranked triamcinolone as the most effective single treatment with 82.2% scar reduction on the Vancouver Scar Scale.

Combination Intralesional Therapies

TAC Combined with 5-Fluorouracil

The combination of triamcinolone acetonide with 5-fluorouracil has emerged as a superior treatment approach across multiple studies.

Study	Comparison	Efficacy Rate TAC+5-FU	Efficacy Rate TAC Alone	p-value

Study	Comparison	Efficacy Rate TAC+5-FU	Efficacy Rate TAC Alone	p-value
F. A. Khalid et al., 2019	TAC vs. TAC+5-FU	77.2%	49.0%	p=0.002
M. A. Khan et al., 2014	TAC vs. TAC+5-FU	84% good-excellent	68% good-excellent	Not specified
Comparison trial 2022	TAC vs. TAC+5-FU	93.3%	63.3%	p=0.005
Ripala Acharya et al., 2024	TAC vs. TAC+5-FU	Greater ≥50% height reduction	Lesser reduction	Significant
X. J. Liu et al., 2020	TAC vs. TAC+5-FU	RR=1.28 for effectiveness	Reference	p<0.01

Meta-analyses consistently demonstrate the superiority of combination therapy. Mavilakandy et al. found that combination TAC+5-FU was superior to TAC monotherapy (OR 3.45, 95% CI: 2.22-5.35, p<0.00001) and to 5-FU monotherapy (OR 4.17, 95% CI: 2.21-7.87, p<0.0001). The network meta-analysis by I-Chang Lai et al. confirmed that TAC+5-FU achieved the most consistent improvements in treatment efficacy and recurrence control.

Recurrence rates were notably lower with combination therapy. F.A. Khalid et al. reported recurrence in 39.2% of patients receiving TAC alone compared to only 17.5% with TAC+5-FU at 22-month follow-up. Similarly, X.J. Liu et al. found significantly lower recurrence with combination therapy (RR=0.25, 95% CI: 0.14-0.44, p<0.01).

The optimal dilution ratio for TAC and 5-FU combination appears to be 9:1 (5-FU:TAC), which produced the highest standardized mean reduction of 64.1% (95% CI: 60.8-67.5%).

TAC Combined with Botulinum Toxin A

Emerging evidence supports the combination of TAC with botulinum toxin type A (BTA).

Study	Intervention	VSS Improvement	Efficacy Assessment
Jianzhen Shi et al., 2024	BTA+TAC	WMD=-1.46 (95% CI: -1.90 to -1.02)	RR=1.28 (95% CI: 1.14-1.44)
Sha Yang et al., 2021	TAC+BTA	SUCRA: 82.2%	Highest ranked combination
Y. M. Neinaa et al., 2021	BTX-A vs. TAC	Significant VSS improvement	Superior to TAC

The network meta-analysis by Sha Yang et al. ranked TAC+BTA as the most effective combination therapy with a SUCRA score of 82.2%, followed by TAC+5-FU at 69.8%. Botulinum toxin A ranked highest in treatment response but did not significantly reduce recurrence risk when used alone.

Triple Combination Therapies

Triple combination approaches incorporating TAC, 5-FU, and additional modalities show enhanced efficacy.

Study	Triple Combination	Comparison	Outcome
A. Asilian et al., 2006	TAC+5-FU+PDL	TAC alone	75% vs. 20% good-excellent response
Alexandra F. Chandra et al., 2025	TAC+5-FU+PDL	TAC alone	RR 2.98 (95% CI: 1.26-7.02)

Study	Triple Combination	Comparison	Outcome
T. S. K. Menon et al., 2025	TAC+5-FU+hyaluronidase	TAC alone	54.55% vs. 36.65% VSS improvement
M. Ellis et al., 2020	Surgery+radiation+third intervention	Surgery+radiation	7.7% vs. 18.7% recurrence

Asilian et al. demonstrated that TAC+5-FU+PDL produced 75% good-to-excellent improvements compared to only 20% with TAC alone. The combination was also more acceptable to patients and produced better cosmetic outcomes, particularly in lightening erythema.

Verapamil vs. Triamcinolone Acetonide

Multiple studies have compared verapamil with TAC as intralesional agents.

Study	Efficacy Finding	Safety Finding
Wei Zhang et al., 2022	TAC superior for vascularity, height (≤9 weeks), pliability (≤18 weeks)	Verapamil had fewer adverse events
Zhengying Jiang et al., 2020	TAC improved pliability and vascularity more after 3 weeks ($p<0.05$)	Verapamil had fewer skin atrophy cases
Jing Kuang et al., 2021	Triamcinolone better efficacy ($p<0.05$)	Verapamil more safe
Ruiquan Liu et al., 2020	No significant differences in VSS parameters	Lower telangiectasia and skin atrophy with verapamil

Study	Efficacy Finding	Safety Finding
Asma Batool et al., 2025	TAC more effective (p<0.001)	Pain in almost all patients with both

The meta-analysis by Wei Zhang et al. found that while TAC produced faster improvements in height, pliability, and vascularity, verapamil showed superior results for pliability between 18 and 24 weeks of treatment. Verapamil consistently demonstrated a better safety profile with significantly lower incidence of skin atrophy (RR=0.13, 95% CI: 0.04-0.42), telangiectasia (RR=0.08, 95% CI: 0.02-0.28), and hyperpigmentation (RR=0.12, 95% CI: 0.03-0.44).

5-Fluorouracil Monotherapy

5-Fluorouracil as monotherapy has shown variable results compared to TAC.

Study	5-FU Outcome	TAC Outcome	Comparison
A. Prabhu et al., 2012	57.48% size reduction	71.23% size reduction	TAC superior (p=0.04)
M. Shah et al., 2014	86.33% size reduction	66.66% size reduction	5-FU superior
B. Shah et al., 2024	70.9% efficacy	50.6% efficacy	5-FU superior (p=0.009)
A. Sadeghinia et al., 2012	More significant improvement	Less improvement	5-FU tattooing superior (p<0.05)
Aliyah King et al., 2024	73% achieved >25% improvement; 67% achieved >50% improvement	Reference	Consistent improvement

The systematic review by Aliyah King et al. encompassing 2,325 patients found that 5-FU monotherapy demonstrated consistent keloid improvement with 73% of patients experiencing greater than 25% improvement and 67% achieving greater than 50% improvement. The relapse rate was 16% at 27 weeks.

Laser Therapies

Fractional CO2 Laser

Fractional carbon dioxide laser has emerged as an effective treatment modality, particularly when combined with adjuvant therapies.

Study	Intervention	VSS Outcome	Other Findings
Christophe Abi Zeid Daou et al., 2025	FCO2 monotherapy	Significantly better VSS scores vs. other lasers	No difference in patient satisfaction
J. Foppiani et al., 2024	FCO2+5-FU	MD=-5.97 (95% CI: -7.30 to -4.65)	Most effective for VSS and thickness
Niti Tawaranurak et al., 2022	FCO2+topical TA	59.1% scar volume change	Intralesional TA achieved 86.5%
Bassel Younes et al., 2025	FCO2 alone vs. FCO2+5-FU/TAC	All groups showed significant improvement	No difference between 5-FU and TAC

The network meta-analysis by Foppiani et al. found that FCO2 plus 5-FU was the most effective intervention for decreasing VSS scores (MD=-5.97, 95% CI: -7.30 to -4.65) and thickness (MD=-2.22, 95% CI: -3.13 to -1.31).

Pulsed Dye Laser and Other Lasers

Study	Laser Type	Outcome
B. Worley et al., 2023	Ablative and PDL	Most useful laser treatments for keloids
Mohamed M. Khedr et al., 2019	Nd:YAG vs. E-light	E-light showed better response ($p<0.001$)
S. A. Rahman et al., 2020	Nd:YAG ± steroid/BTA	Combination with steroid showed highest improvements
Yiqiu Zhang et al., 2023	CO2+IPL vs. IPL	Combination superior in itching, color, stiffness, thickness

Laser treatment response appears linked to Fitzpatrick skin type, with significantly better outcomes for types I-III compared to types IV-VI ($p=0.002$). This represents an important consideration for treatment selection in patients with darker skin types.

Surgical Excision with Adjuvant Therapy

Surgical excision alone carries high recurrence rates of 45-100%, necessitating adjuvant therapy.

Surgery with Radiotherapy

Study	Protocol	Recurrence Rate	Follow-up
M. V. van Leeuwen et al., 2014	Excision + 2×6 Gy brachytherapy	3.1%	33.6 months
Siqi Fu et al., 2023	Excision + radiotherapy	13.5% (95% CI: 6.6-22.2%)	Variable

Study	Protocol	Recurrence Rate	Follow-up
M. V. van Leeuwen et al., 2015	HDR brachytherapy	Lower than LDR or external	Mean 15 months recurrence
Ru Wang et al., 2021	Surgery + radiotherapy	RR 0.43 vs. corticosteroid (95% CI: 0.21-0.89)	Variable

High-dose-rate brachytherapy with a short time interval (<7 hours) between excision and irradiation produces lower recurrence rates compared to longer intervals. The unique protocol of 2×6 Gy administered within 4 and 24 hours post-surgery achieved only 3.1% recurrence at mean 33.6-month follow-up.

Surgery with Intralesional Injections

Study	Protocol	Efficacy	Comparison
F. A. Khalid et al., 2018	Excision + 5-FU/TAC	73.33% efficacy	Superior to excision + radiotherapy (43.33%)
Yazhuo Li et al., 2022	Excision + 5-FU/betamethasone	No significant difference vs. excision + radiotherapy	Superior to intralesional alone
Yasir T. Radhi et al., 2025	Debulking + TAC	13.3% recurrence	92.3% recurrence with debulking alone

Debulking combined with intralesional TAC demonstrated dramatically reduced recurrence (13.3%) compared to debulking alone (92.3%), with significantly higher patient satisfaction scores (8.6 vs. 3.5).

Physical and Topical Therapies

Pressure Therapy and Silicone

Study	Intervention	Outcome
C. Li-Tsang et al., 2010	Pressure + silicone vs. pressure alone	Combined therapy more effective for thickness after 2 months ($p<0.001$)
Peixuan Zhang et al., 2023	Pressure + silicone vs. pressure alone	PTS superior for height (MD=0.15, $p<0.01$) and pliability (MD=0.35, $p<0.01$)
B. Worley et al., 2023	Silicone sheeting	SMR 29.9% (95% CI: 28.9-30.9%)
Kierra Jackson et al., 2025	Early vs. late PGT	Early: 30.2% reduction; Late: 4.5% reduction

Physical treatments including silicone sheeting demonstrated a standardized mean reduction of 29.9%, while topical treatments achieved 34%, both substantially lower than intralesional injection at 64.1%. Early intervention with pressure garment therapy (30.2% reduction) was significantly more effective than late intervention (4.5%).

Cryotherapy

Study	Intervention	Outcome
C. Zouboulis et al., 2020	Cryosurgery ± TAC	83.3-90% good-excellent responses

Study	Intervention	Outcome
B. Behera et al., 2016	CO2 laser + TAC vs. cryotherapy + TAC	No significant difference at 12 months
Sadia Abbasi et al., 2025	TAC + cryotherapy vs. TAC alone	81.5% vs. 60.5% efficacy (p=0.038)

Cryosurgery was effective on young (<2 years old), small (≤10 cm^2) keloids, with marked flattening achieving median lesional volume decreases from 106-138 mm^3 to 6-7 mm^3. Combination with intralesional corticosteroids enhanced outcomes.

Novel and Emerging Therapies

Platelet-Rich Plasma

Study	Intervention	Finding
E. S. Hewedy et al., 2020	TAC + PRP vs. TAC alone	Better improvement in height, pigmentation, pliability
Y. M. Neinaa et al., 2021	PRP vs. TAC	Significant VSS improvement; better cosmetic outcomes
Alireza Jafarzadeh et al., 2023	PRP (various studies)	Effective with minimal side effects

PRP combined with TAC yielded cosmetically better outcomes with lower incidence of TAC-induced side effects, particularly atrophy and hypopigmentation.

Vitamin D

Study	Comparison	Efficacy	Safety

Study	Comparison	Efficacy	Safety
Aman Goyal et al., 2024	Vitamin D vs. TAC	50% vs. 76.7% achieved >50% VSS reduction	Fewer adverse effects with vitamin D
Aman Goyal et al., 2023	Vitamin D vs. TAC	Comparable reduction in VSS scores	Lower hypopigmentation (37% vs. 80%) and atrophy (40% vs. 73%)

Intralesional vitamin D demonstrated lower efficacy than TAC but significantly better safety, making it a potential alternative for patients who cannot tolerate corticosteroid side effects.

Bleomycin

Study	Intervention	Outcome
Koorosh Ahmadpour et al., 2006	Bleomycin tattoo vs. cryotherapy + TAC	Superior for larger lesions (>100 mm^2) (p=0.03)
Alexandra F. Chandra et al., 2025	TAC + bleomycin	Lowest recurrence (RR 0.04, 95% CI: 0.00-0.84)

Bleomycin tattooing showed particular effectiveness for larger lesions (>100 mm^2), with mean resolution scores of 88.3±14 compared to 67.3±22.5 for cryotherapy combined with TAC (p=0.001).

Safety Profiles

Adverse Events by Treatment Modality

Treatment	Common Adverse Events	Incidence
TAC	Skin atrophy	44%
TAC	Telangiectasia	50%
TAC	Hypopigmentation	80%
5-FU	Skin ulceration	Common in 5-FU group
5-FU	Burning sensation	Higher incidence
Verapamil	Skin atrophy	RR=0.13 vs. TAC
Verapamil	Telangiectasia	RR=0.08 vs. TAC
TAC+5-FU	Overall complications	Lower than TAC alone
Bleomycin	Hyperpigmentation	75% (temporary)

TAC at concentrations of 20 mg/mL or 40 mg/mL was more likely to result in skin atrophy compared to 5-FU or verapamil, and more likely to cause telangiectasia than 5-FU, 5-FU+TAC, or bleomycin. The combination of TAC with 5-FU demonstrated lower overall complication rates compared to TAC alone ($p<0.05$).

Verapamil consistently demonstrated the best safety profile across studies, with significantly lower incidence of skin atrophy, telangiectasia, and hyperpigmentation, though it was associated with a higher incidence of burning sensation.

For laser treatments, adverse events were generally uncommon and mostly transient. Specific complications included charring with CO2 laser, while surgical excision with radiotherapy showed relatively low incidence of atrophy (0.0%), telangiectasia (3.2%), and erythema (2.3%).

Synthesis

Reconciling Apparent Contradictions in Treatment Efficacy

The evidence presents several apparent contradictions that require careful interpretation through examination of study characteristics and treatment contexts.

TAC vs. 5-FU Monotherapy Discrepancies

Studies comparing TAC and 5-FU monotherapy yielded conflicting results: Prabhu et al. found TAC superior (71.23% vs. 57.48% reduction, p=0.04), while Shah et al. found 5-FU superior (70.9% vs. 50.6% efficacy, p=0.009), and M. Shah et al. also favored 5-FU (86.33% vs. 66.66%).

These differences likely reflect variations in treatment protocols rather than true therapeutic inconsistencies. The concentration of 5-FU (45-50 mg/mL) and injection technique varied across studies. Additionally, Lin et al. demonstrated that 5-FU efficacy was dose-dependent, with high-concentration 5-FU (12.5 mg/mL combined with TAC) showing significantly better outcomes than medium (5.0 mg/mL) or low (0.5 mg/mL) concentrations. Patient satisfaction scores were 88±8 for high concentration versus 60±8 for low concentration.

Verapamil Efficacy Variations

The comparison between verapamil and TAC shows verapamil is consistently less effective in the short term (first 3 weeks), but may achieve comparable results with longer treatment duration. Wei Zhang et al. found verapamil produced superior pliability results between 18 and 24 weeks. This temporal pattern suggests verapamil has a slower mechanism of action but may be appropriate for extended treatment courses where TAC side effects become limiting.

Context-Specific Treatment Selection

The evidence supports different treatment selections based on specific clinical contexts:

For **rapid response with larger keloids**, intralesional TAC or TAC+5-FU combination is most appropriate, achieving standardized mean reduction of 64.1% and superior efficacy rates of 77-93%.

For **cosmetically sensitive areas**, 5-FU may be preferable due to lower rates of skin atrophy (8% vs. 44%) and telangiectasia (21% vs. 50%).

For **patients with Fitzpatrick skin types IV-VI**, laser therapy should be approached cautiously, as treatment response was significantly linked to skin type ($p=0.002$), with better outcomes for types I-III.

For **recalcitrant lesions**, surgical excision with adjuvant high-dose-rate brachytherapy achieves the lowest recurrence rates (3.1%), particularly when the radiation is administered within 7 hours of surgery.

For **young, small keloids (<2 years, ≤10 cm²)**, cryosurgery with or without intralesional corticosteroids is effective and safe, achieving 83-90% good-to-excellent responses.

For **larger lesions (>100 mm²)** where other treatments have limited efficacy, bleomycin tattooing demonstrates superior effectiveness compared to cryotherapy with TAC ($p=0.03$).

Combination vs. Monotherapy

The evidence strongly supports combination approaches over monotherapy. Network meta-analyses consistently rank combination therapies highest: TAC+BTA (SUCRA 82.2%) > TAC+5-FU (69.8%) > BTA alone (67.3%) > 5-FU alone (49.8%) > TAC alone (26.7%). The combination of TAC+5-FU achieves both superior efficacy and lower complication rates, representing the best balance for most clinical scenarios.

For surgical cases, triple therapy (surgery plus two or more adjuvant interventions) achieved significantly lower recurrence (7.7%) compared to dual therapy (18.7%) when radiation was

included (p=0.002). This suggests that multimodal approaches targeting different pathogenic mechanisms produce synergistic benefits.

DISCUSSION

This comprehensive synthesis of 80 studies elucidates the complex landscape of keloid and hypertrophic scar management, revealing clear hierarchies in treatment efficacy, safety considerations, and the critical importance of combination strategies.

Superiority of Combination Therapies: The most compelling finding is the consistent superiority of combination therapies over monotherapies. The combination of triamcinolone acetonide (TAC) and 5-fluorouracil (5-FU) emerged as a cornerstone of effective treatment. Meta-analyses demonstrate significantly higher efficacy rates for TAC+5-FU (77.2–93.3%) compared to TAC alone (49.0–68%) (Khalid et al., 2019; Khan et al., 2014; Liu et al., 2020). This combination also substantially reduces recurrence rates; for instance, recurrence was 39.2% with TAC alone versus 17.5% with TAC+5-FU at 22-month follow-up (Khalid et al., 2019). The mechanistic rationale is sound: TAC inhibits inflammation and fibroblast proliferation, while 5-FU, an antimetabolite, inhibits collagen synthesis and fibroblast activity, providing a synergistic effect (Mavilakandy et al., 2023).

Furthermore, network meta-analyses provide a nuanced ranking of therapies. Sha Yang et al. (2021) ranked TAC combined with botulinum toxin A (BTA) highest (SUCRA 82.2%), followed by TAC+5-FU (69.8%). BTA is thought to reduce scar tension and microtrauma from muscle movement, enhancing drug delivery and reducing mechanical stress on the scar (Shi et al., 2024; Neinaa et al., 2021). Triple therapies push efficacy further. Asilian et al. (2006) demonstrated that TAC+5-FU+pulsed-dye laser (PDL) yielded 75% good-to-excellent responses versus 20% with TAC alone. The PDL targets scar vasculature, reducing erythema and improving drug penetration. Similarly, surgical excision followed by dual adjuvant therapy (e.g., radiation + intralesional injection) achieves lower recurrence (7.7%) than surgery with a single adjuvant (18.7%) (Ellis et al.,

2020). This underscores a fundamental principle: multimodal approaches that attack different aspects of scar pathogenesis—inflammation, fibrosis, angiogenesis, and mechanical tension—produce superior and more durable outcomes.

Reconciling Monotherapy Discrepancies: Apparent contradictions in the literature, particularly regarding TAC versus 5-FU monotherapy, can be reconciled by examining study protocols. Prabhu et al. (2012) found TAC superior (71.23% vs. 57.48% reduction), while Shah et al. (2024) and M. Shah et al. (2014) found 5-FU superior. These differences likely stem from variations in 5-FU concentration, injection technique, and scar characteristics. Lin et al. (2021) demonstrated a clear dose-response relationship for 5-FU, with high concentration (12.5 mg/mL with TAC) achieving significantly better outcomes and patient satisfaction (88±8) than low concentration (60±8). This highlights that reported efficacy is not solely agent-dependent but profoundly influenced by technical execution and dosage.

Safety Profiles and Therapeutic Trade-offs: Safety is a paramount consideration influencing treatment choice. TAC, while effective, carries a high burden of local adverse effects, including skin atrophy (44%), telangiectasia (50%), and hypopigmentation (80%) (Zhang et al., 2022; Batool et al., 2025). These effects are dose- and concentration-dependent. In contrast, verapamil exhibits a markedly superior safety profile, with significantly lower risks of atrophy (RR=0.13), telangiectasia (RR=0.08), and hyperpigmentation (RR=0.12) compared to TAC (Zhang et al., 2022; Liu et al., 2020). However, its efficacy manifests more slowly, often requiring 18–24 weeks to match TAC's effects on pliability (Zhang et al., 2022). This trade-off positions verapamil as an excellent option for patients intolerant to steroid side effects, particularly in cosmetically sensitive areas, provided extended treatment is feasible.

Novel agents like intralesional vitamin D offer another safer alternative, though with lower efficacy (50% >50% VSS reduction) than TAC (76.7%) (Goyal et al., 2024). Its significantly lower rates of hypopigmentation and atrophy make it viable for steroid-sensitive patients. Platelet-rich plasma (PRP), often combined with TAC, improves scar texture and vascularity while potentially

mitigating TAC-induced side effects, leading to better cosmetic outcomes (Hewedy et al., 2020; Jafarzadeh et al., 2023).

Contextual Treatment Selection: The evidence strongly advocates for a personalized, context-driven approach:

- **Rapid reduction of large keloids:** TAC+5-FU is first-line, offering a high standardized mean reduction of 64.1% (Mavilakandy et al., 2023).
- **Cosmetically sensitive areas (face, décolletage):** 5-FU or verapamil may be preferable due to lower atrophy risk.
- **Recalcitrant scars:** Surgical excision with immediate adjuvant high-dose-rate brachytherapy (within 7 hours) offers the lowest recurrence rates (~3.1%) (van Leeuwen et al., 2014).
- **Young, small keloids (<2 years, ≤10 cm²):** Cryosurgery, especially combined with intralesional steroids, is highly effective (83–90% good-excellent response) (Zouboulis et al., 2020).
- **Hypertrophic scars (especially post-burn):** Early intervention with silicone gel sheeting and pressure therapy is foundational, with combination pressure+silicone being more effective than pressure alone (Li-Tsang et al., 2010; Zhang et al., 2023).
- **Darker skin types (Fitzpatrick IV-VI):** Laser therapies require caution, as response is significantly better in lighter skin types (p=0.002). Nd:YAG or fractional non-ablative lasers may be safer initial choices than aggressive ablative CO_2 (Rahman et al., 2020; Foppiani et al., 2024).

Limitations and Future Directions: This synthesis is constrained by the limitations of the included studies, such as heterogeneous methodologies, variable follow-up durations, and a lack of

standardized outcome measures. Long-term recurrence data (>5 years) for many newer combinations are sparse. Future research must prioritize large, well-designed RCTs with standardized protocols, direct head-to-head comparisons of leading combinations (e.g., TAC+5-FU vs. TAC+BTA), and cost-effectiveness analyses. Investigating patient-reported outcomes and quality of life measures is equally crucial. Furthermore, exploring the molecular basis of scar heterogeneity could pave the way for truly personalized, targeted therapies.

The management of keloids and hypertrophic scars has evolved from a trial of monotherapies to a strategic, multimodal paradigm. Combination therapy, particularly TAC+5-FU, stands as the most evidence-based, effective, and balanced approach for the majority of cases. Ultimate success depends on the clinician's ability to tailor this growing arsenal of tools to the individual's scar morphology, location, skin type, and treatment goals.

CONCLUSION AND RECOMMENDATIONS

Conclusion

Summary of Findings: This extensive evidence synthesis demonstrates that the treatment of keloids and hypertrophic scars is most effectively approached through combination therapies. Triamcinolone acetonide combined with 5-fluorouracil (TAC+5-FU) represents the most consistently effective and well-supported regimen, offering superior scar reduction, lower recurrence rates, and a more favorable safety profile compared to TAC monotherapy. Other potent combinations include TAC with botulinum toxin A and triple therapies incorporating laser or surgical modalities. Verapamil emerges as a safer, albeit slower-acting, alternative to corticosteroids. The efficacy of physical and laser therapies is enhanced when used as adjuvants to intralesional or surgical treatments. Treatment outcomes are highly dependent on specific scar characteristics (age, size, location) and patient factors (skin type, tolerance to side effects).

Recommendations:

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1. **First-line therapy:** For most keloids and hypertrophic scars, initiate treatment with combination intralesional TAC and 5-FU.
2. **Personalized approach:** Tailor treatment based on:
    - **Scar type/location:** Use 5-FU or verapamil in cosmetically sensitive areas; consider surgery + radiotherapy for recalcitrant ear or sternal keloids.
    - **Patient profile:** Choose verapamil or vitamin D for patients with high risk of steroid atrophy; exercise caution with lasers in darker skin types.
    - **Scar chronicity & size:** Employ cryotherapy for young, small keloids; consider bleomycin for larger lesions (>100 mm^2).
3. **Adopt multimodal strategies:** Do not rely on monotherapy for complex scars. Combine surgical, pharmacological, and physical modalities to target different pathological pathways.
4. **Prioritize safety monitoring:** Actively monitor for local adverse effects, especially skin atrophy and hypopigmentation with corticosteroids, and adjust treatment accordingly.
5. **Future research:** The field requires standardized treatment protocols, long-term follow-up studies, and RCTs directly comparing the top combination therapies to establish clear hierarchical guidelines.

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