

Safety and Efficacy of Tacrolimus Ointment Alone in the Treatment of Pediatric Vitiligo: A Systematic Review and Meta-Analysis

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Keywords

Demography · Dermatology · Meta-analysis · Pediatric case · Tacrolimus · Vitiligo

Abstract

Introduction: Vitiligo, a skin disorder affecting melanocytes, poses treatment challenges. There is a need to investigate the role of tacrolimus in pediatric cases for its efficacy and safety. The present study aimed to assess the safety and efficacy of tacrolimus ointment in treating pediatric vitiligo patients. **Methods:** A review study was conducted, and a literature search was done on 2 August 2023, by using the words “vitiligo” and “tacrolimus” through five databases including PubMed. We found 8 studies from 930 records. **Results:** The rates of excellent, moderate, mild, minimal improvement, and no response were 29% (95% CI: 16–47), 26% (95% CI: 19–35), 28% (95% CI: 20–37), 19% (95% CI: 12–29), and 8% (95% CI: 2–25). No systemic side effects were reported. The overall prevalence of local side effects was 14% (95% CI: 7–24). Burning sensation prevalence was 11% (95% CI: 7–18), while pruritus prevalence was 9% (95% CI: 2–33). Study limitations encompassed varied vitiligo sites, patient demographics, and follow-up durations, lacked comparative treatment data, and necessitated further research on

combined therapies, especially in pediatric cases. **Conclusion:** Tacrolimus showed good efficacy regarding the re-pigmentation improvement in pediatric vitiligo patients. Furthermore, no systemic side effects were reported and local side effects were minimal mainly in the form of a burning sensation and pruritus.

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Introduction

Vitiligo is a common skin disorder that affects the melanocytes leading to a characteristic skin lesion that has a different skin color other than the skin color of the entire body. The pathogenicity of vitiligo stems from several genetic, environmental, and metabolic abnormalities [1]. Vitiligo prevalence ranged from 0.05 to 2%; however, the meta-analysis of 82 pooled studies indicated that the vitiligo prevalence was 2% and Africa had the highest prevalence of vitiligo with a prevalence of 4% [2].

Vitiligo treatment is considered a major problem among the dermatologic society due to the long treatment period, treatment relapse, and resistance to treatment in certain body areas such as lips and distal extremities [3]. There are many treatment strategies for vitiligo treatment

aiming to obtain the skin color of the depigment lesion to reach the same color as the surrounding skin color. Surgery, topical and systemic immune suppressants, and phototherapy are the common treatment options; the latter has the highest efficacy among them especially if combined with another treatment option [4].

Vitiligo manifests as pale patches caused by a reduction in melanocytes within the skin and hair follicles. This condition can emerge at any point in life, impacting approximately 2% of the overall population regardless of gender and, in certain areas [5]. Its effects on patients' lives are substantial, significantly affecting their well-being. Unfortunately, available treatments fall short of delivering complete satisfaction due to the unpredictability of progress, lengthy treatment durations, potential side effects, and the challenges associated with applying medications [5].

The primary treatment for vitiligo continues to be topical corticosteroids. However, there are significant concerns regarding the side effects that arise from prolonged corticosteroid application, such as telangiectasia and skin atrophy. These effects on the skin are a major area of concern for those undergoing long-term corticosteroid treatments [6]. It is believed that vitiligo primarily stems from an autoimmune process where certain immune cells, particularly lymphocytes, mistakenly attack melanocytes [6]. This theory has led to the exploration of treatments involving immunomodulatory substances like tacrolimus. Originally designed for managing atopic dermatitis, tacrolimus ointment operates by suppressing the generation of pro-inflammatory cytokines. Through topical administration, tacrolimus exhibits potential in revitalizing areas affected by vitiligo, offering hope for repigmentation in these regions [7].

Tacrolimus exhibits high effectiveness in patients experiencing the progression phase of vitiligo [8]. However, its efficacy appears to be comparatively lower when applied to segmental vitiligo and lesions that manifest in infancy or early stages of development [9]. Tacrolimus is reported to be an approved immunomodulator for the treatment of vitiligo which the drug inhibits the activation and the maturation of T cells [10]. Since the last two decades, there has been a noticeable increase in interest regarding the application of topical tacrolimus therapy for treating vitiligo [11]. Many studies have discussed the role of tacrolimus in the treatment of vitiligo in the pediatric population [12–14]. Herein, we aimed to conduct a meta-analysis to determine the safety and efficacy of tacrolimus in the treatment of pediatric vitiligo patients.

Material and Methods

Information Sources

This study adhered to the PRISMA guidelines for reporting the findings of the systematic review and conducting the meta-analysis [15].

Eligibility Criteria

We included papers that investigated the safety and efficacy of tacrolimus ointment alone in the treatment of pediatric vitiligo (<18 years old). However, papers that reported the combination of tacrolimus and other therapeutic agents, adult patients (>18 years old), reviews, conference papers, and case reports <10 patients were excluded. Due to the author's proficiency in the English language only, the articles written in English were considered suitable for inclusion in this study. Articles lacking quantitative data were excluded from the scope of this current analysis.

Search Strategy

On 2 August 2023, a literature search was conducted by using the words “vitiligo” and “tacrolimus” through databases including PubMed, Google Scholar, Embase, and Medline and listed in the flowchart for this systematic review. This search was refined to include articles from a defined 20-year period, including publications between 2003 and 2023. No other filters were applied to the search.

The process of selecting academic papers started with collecting records from various databases: PubMed (226 records), Scopus (246 records), Web of Science (346 records), Virtual Health Library (VHL, 264 records), and Google Scholar. These records are then imported into EndNote X9.0.1 for management. First, duplicate records are identified and removed, resulting in 930 unique records (389 duplicates were excluded). Title and abstract screening were done for 930 records, of which 907 records were excluded and 23 records were further screened via the full texts. We found 6 papers from the screening step. Further 2 articles were included by manual search of references from the included papers. Based on this screening, a total of 8 were included to conduct a meta-analysis (shown in Fig. 1) [12–14, 16–20].

Study Selection and Data Collection

Two authors independently conducted data selection. Initially, article titles underwent manual screening for relevance to the research. Abstracts meeting the study's focus proceeded to full-text assessment. Articles lacking full text were excluded. Bibliographies were manually

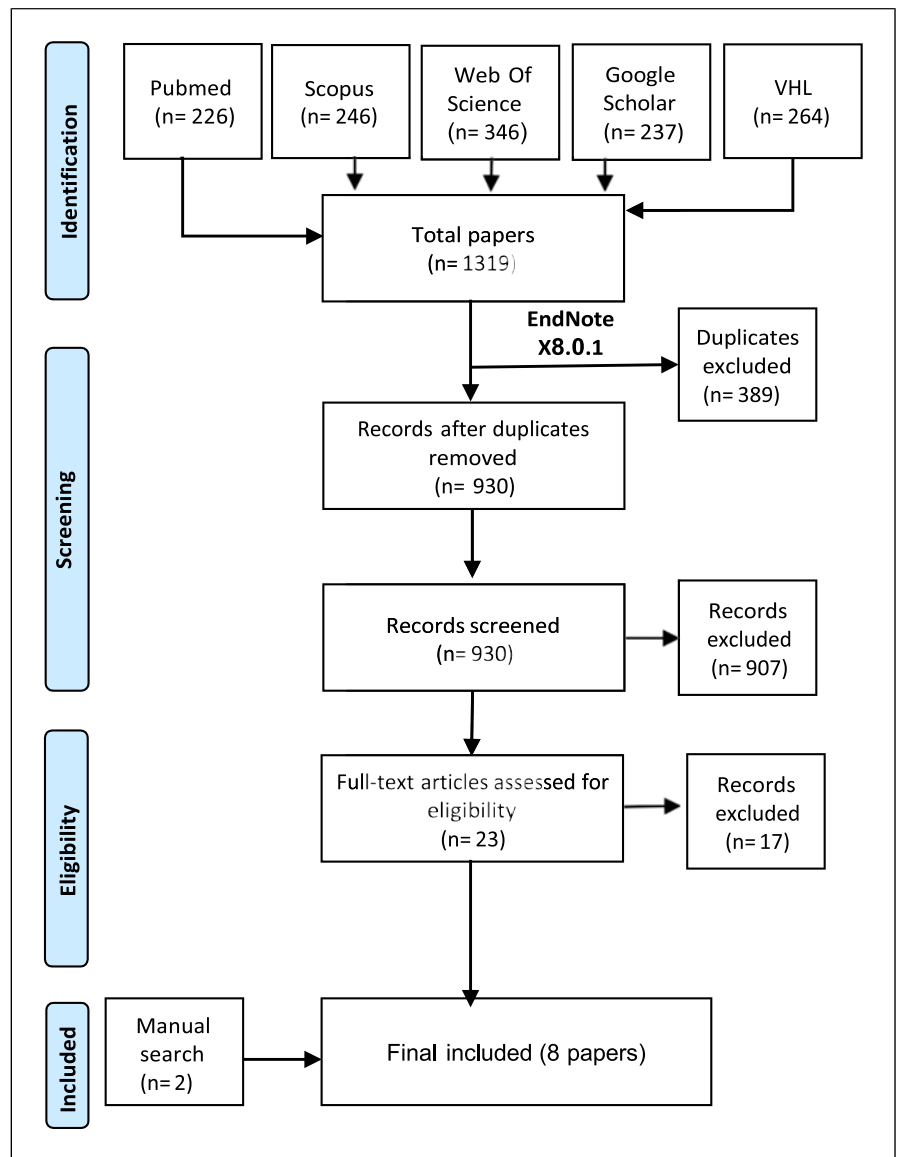


Fig. 1. PRISMA flow diagram of the study process: the selection process of articles, starting from 930 initial records, screening, and culminating in 8 studies included in the meta-analysis.

screened to identify pertinent studies. All selected articles underwent evaluation and inclusion discussions among the researchers.

One author gathered all the resulting records from the five databases and exported them to an Excel sheet after removing duplicated records by Endnote software. The screening was done by one author, and another author revised the results of this screening. However, only two members scanned the included records via title and abstract and full-text screening.

In case of disagreements between reviewers during the selection and data extraction process, a third senior reviewer was consulted to resolve conflicts. The senior reviewer reviewed the discrepancies and

made the final decision on inclusion or exclusion to ensure consistency and accuracy in the study selection process.

Data Extraction

The senior author made an Excel sheet for screening with the help of the other authors. The sheet included characteristics (study design, study ID, age, female %, tacrolimus dose, and follow-up of patients). The efficacy outcome was reported as improvement in repigmentation (excellent: 75–100%, moderate: 50–75%, mild: 25–50%, minimal: 0–25%, and no response), while the safety outcome was reported as any local or systemic side effects posttreatment use.

Table 1. Characteristics of the included papers.

Study ID	Region	Study design	Sample size	Age	Female, %	Follow-up duration	Dose
Alshiyab et al. [16]	Jordan	RCT	24	<18 ^a	54	9 months	0.1% ointment twice daily
Bhuiyan et al. [17]	Bangladesh	Prospective cohort	30	0–13 ^a	57	12 weeks	0.03% ointment was administered twice daily
Hu et al. [18]	China	RCT	23	<2 ^a		6 months	0.03% ointment was administered twice daily
Ho et al. [19]	Canada	RCT	33	8.4 ^b	52	6 months	0.1% ointment twice daily
Lepe et al. [20]	Mexico	RCT	20	<18 ^a		2 months	0.1% ointment twice daily
Kanwar et al. [12]	India	Prospective cohort	22	7.2 ^b	59	12 weeks	0.03% ointment was administered twice daily
Silverberg et al. [13]	USA	Retrospective cohort	57	9.2 ^b	32	3 months	0.03% and 0.1% ointment was administered twice daily
Sriram et al. [14]	India	RCT	25	2–14 ^a	55	2 years	0.03% ointment was administered twice daily

^aRange. ^bMean.

Risk of Bias Assessment

Two tools for risk of bias were used in our study. The Cochrane risk of bias tool was used in the case of randomized controlled trials (RCTs), and the National Institute of Health tool was used in the case of cohort studies. Further information and score assessment have been reported in online supplementary file (online suppl. Table S1, S2; for all online suppl. material, see <https://doi.org/10.1159/000543311>).

Synthesis Methods

Comprehensive meta-analysis software was used for the analysis. The event rate together with the 95% confidence interval (95% CI) was used to analyze both the safety and efficacy outcomes. If the value of heterogeneity was lower than 0.1 or I^2 was higher than 50, we considered significant heterogeneity and a random model will be run [21]. Additionally, sensitivity analyses were conducted to explore the robustness of the results and subgroup analyses were performed to investigate potential sources of heterogeneity.

Results

Search Results

Five studies were RCTs, two studies were prospective cohorts, and one study was a retrospective cohort with a total sample size in the included papers 234 patients.

Four studies used tacrolimus 0.03% twice daily, three studies used tacrolimus 0.1% twice daily, and in one study we could not get the total number of patients that received 0.1% or 0.03% tacrolimus twice daily. The follow-up was different among the included studies and ranged from 2 months to 2 years. Table 1 presents the summary of the eight included studies evaluated for conducting meta-analysis.

Efficacy

The assessment of treatment efficacy unveiled varying degrees of improvement among patients with vitiligo. Remarkably, nearly a third of individuals (29%, 95% CI: 16–47) showcased excellent improvement, denoting a substantial 75–100% re-pigmentation in affected areas (shown in Fig. 2). Another significant portion, comprising 26% of cases (95% CI: 19–35), experienced moderate improvement, indicating a notable 50–75% re-pigmentation (shown in Fig. 3). Additionally, a considerable 28% (95% CI: 20–37) displayed mild improvement, reflecting a 25–50% re-pigmentation (shown in Fig. 4). However, a noteworthy proportion, accounting for 19% of patients (95% CI: 12–29), demonstrated minimal improvement, ranging from 0 to 25% re-pigmentation (shown in Fig. 5). Intriguingly, 8% of individuals (95% CI: 2–25) exhibited no response to the treatment, indicating no observable improvement in re-pigmentation (shown in

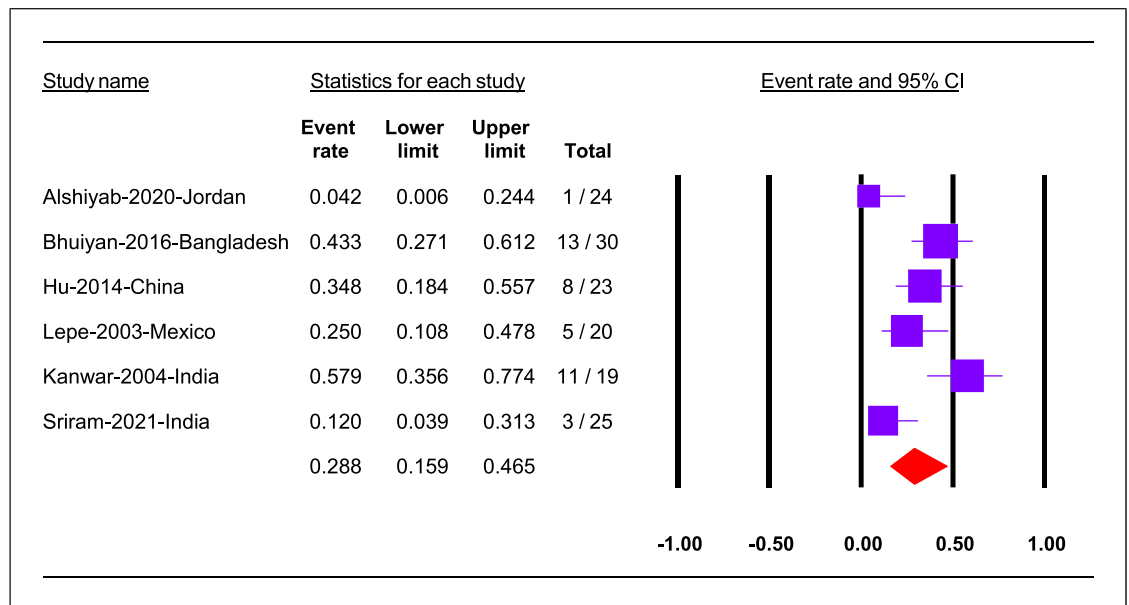


Fig. 2. Excellent improvement in re-pigmentation: the event rate and 95% CI for patients with 75–100% re-pigmentation improvement after tacrolimus treatment, with 29% (95% CI: 16–47) of patients achieving excellent improvement.

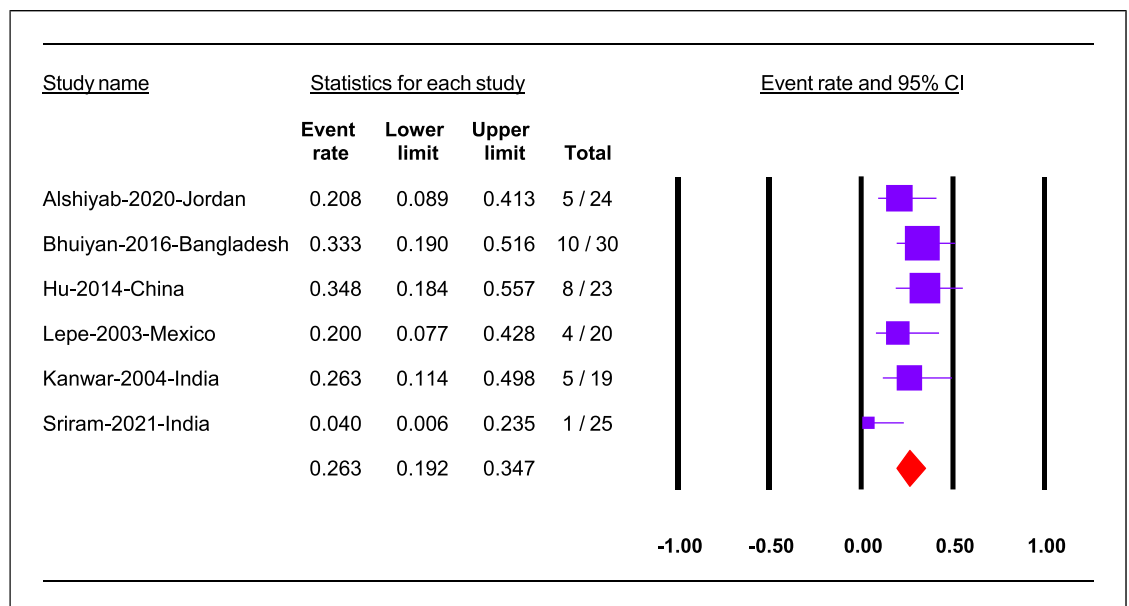


Fig. 3. Moderate improvement in re-pigmentation: the event rate and 95% CI for patients with 50–75% re-pigmentation improvement, indicating that 26% (95% CI: 19–35) of patients had moderate improvement.

Fig. 6). These findings underline the diverse spectrum of responses to the treatment, emphasizing the need for personalized approaches in managing vitiligo based on individual responses and characteristics.

Safety

No systemic side effects were reported. The overall prevalence of local side effects was 14% (95% CI: 7–24) (shown in Fig. 7). Burning sensation prevalence was

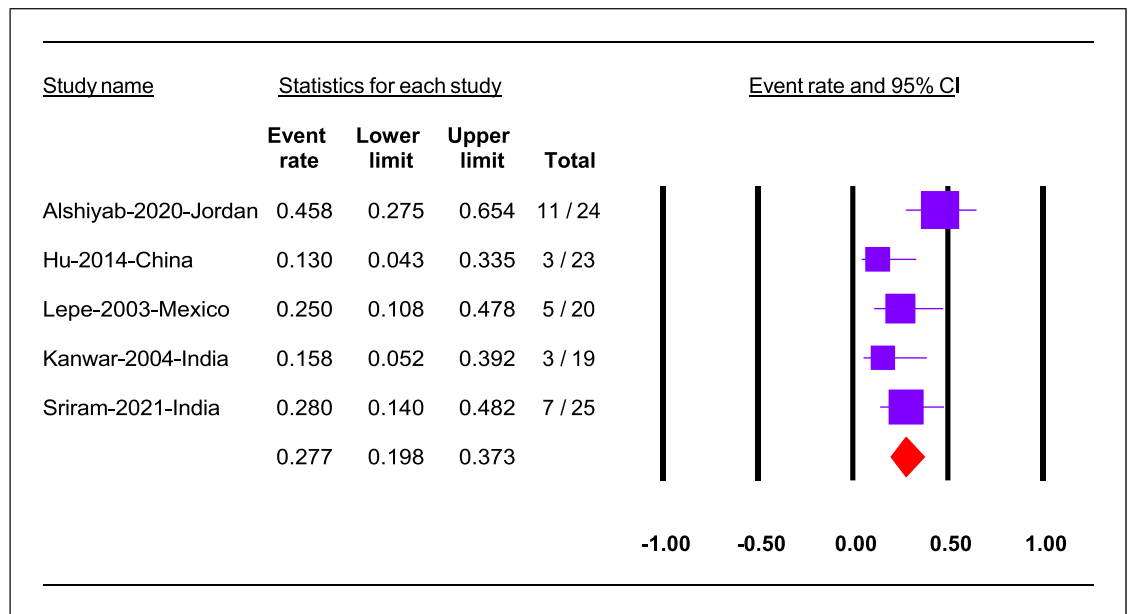


Fig. 4. Mild improvement in re-pigmentation: the event rate and 95% CI for patients with 25–50% re-pigmentation improvement, with 28% (95% CI: 20–37) of patients showing mild improvement.

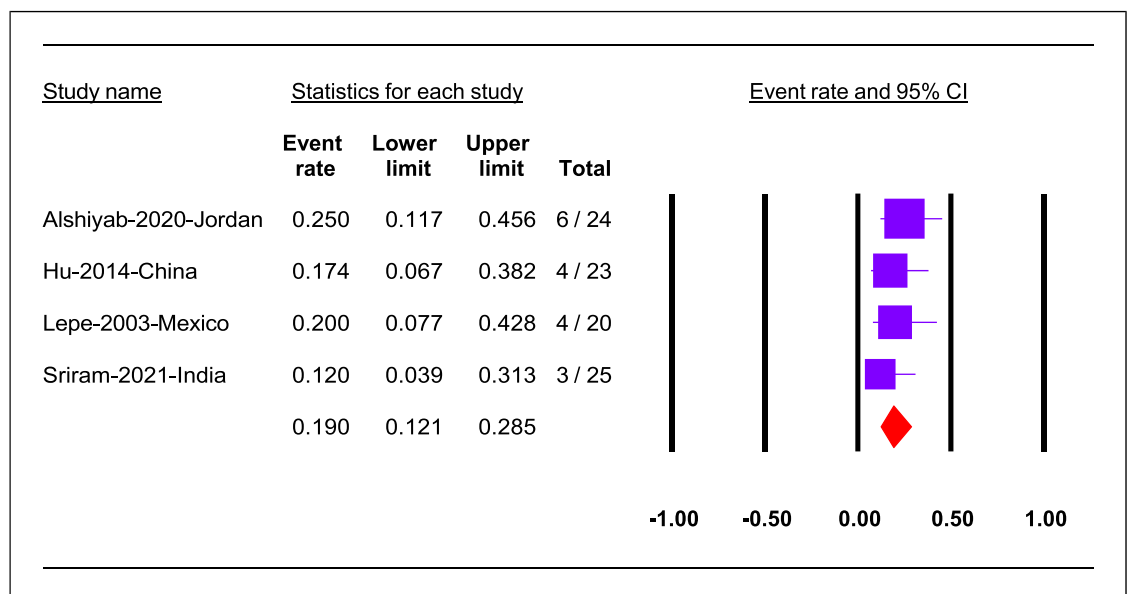


Fig. 5. Minimal improvement in re-pigmentation: the event rate and 95% CI for patients with 0–25% re-pigmentation improvement, showing that 19% (95% CI: 12–29) of patients had minimal improvement.

11% (95% CI: 7–18) (shown in Fig. 8), while pruritus prevalence was 9% (95% CI: 2–33) (shown in Fig. 9). Redness and scratch were reported in 3 patients in one

study, and folliculitis was reported in 1 patient in one study; therefore, they were not included in the meta-analysis [18, 19].

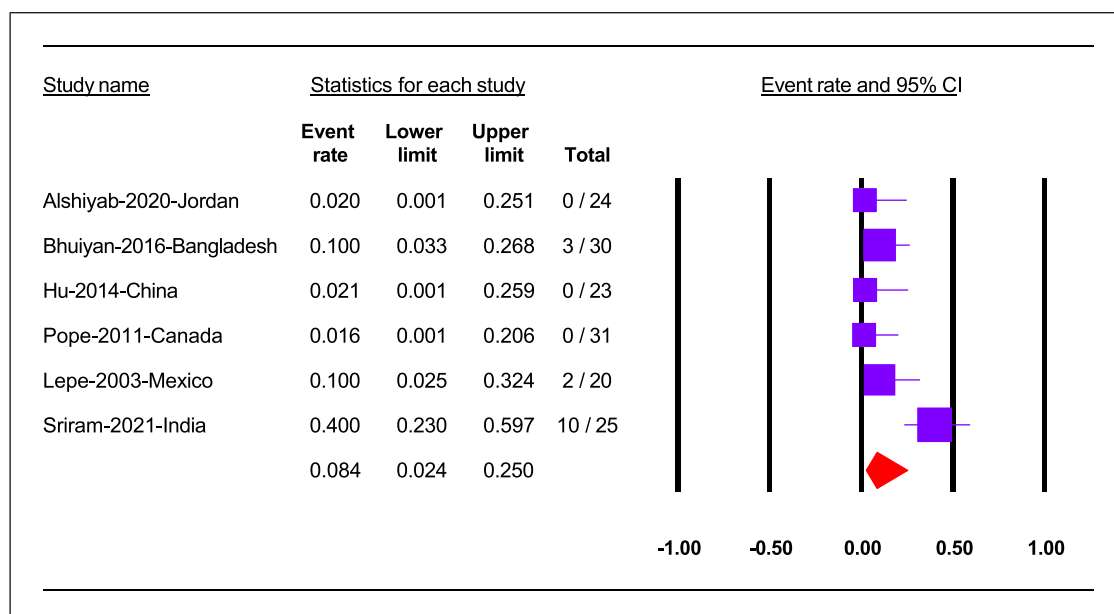


Fig. 6. No response to tacrolimus treatment: the event rate and 95% CI for patients with no re-pigmentation improvement, indicating that 8% (95% CI: 2–25) of patients had no response to the treatment.

Discussion

The hallmark of vitiligo treatment is to attain re-pigmentation of the skin to match the color of the surrounding skin [22]. In our meta-analysis, we found that tacrolimus achieved excellent improvement regarding re-pigmentation in 29% of patients and moderate improvement in 26% of patients. Our results were similar to Lepe et al. [20] which a quarter of patients had an excellent improvement and one-fifth had moderate improvement. The prospective cohort study of Kenwar et al. [12] indicated that 60% of patients had an excellent improvement regarding re-pigmentation. This observation may be due to the short follow-up period of the study (12 weeks) and the small surface area of vitiligo which was reported to be a mean of 2% surface area for all the patients. In contrast to those studies, the RCT of Alshiyab et al. [16] indicated that only 4% of patients had an excellent improvement. One explanation that could be put into consideration is that the follow-up of the study was 9 months where possible relapse or resistance may have occurred [23].

Despite showing promising results in terms of efficacy, many dermatologists questioned whether combining tacrolimus with another treatment strategy could further enhance its effectiveness. Previous published RCT indicated that patients who were randomized to tacrolimus and fractional laser had a

significantly increased prevalence of healing rate of skin defects rather than the control group who was treated with tacrolimus alone [24]. However, the use of different treatment agents as an adjuvant to tacrolimus is still an area of investigation especially in the pediatric age group.

As expected, no systemic adverse events were reported among all patients who were treated with tacrolimus. In addition, a small proportion of patients had adverse events (14%). These adverse events were mainly burning sensations (11%) or pruritus (9%). Furthermore, only two studies reported rare adverse events such as folliculitis, redness, and scratches [18, 19]. Although these events occurred infrequently, it is essential to acknowledge their potential impact on patients' well-being and treatment compliance. In our analysis, the incidence rates of folliculitis, redness, and scratches were reported in only two studies, with rates ranging from low to no significant adverse events [18, 19]. While these adverse events were generally rare and localized, their severity varied among patients, with some experiencing mild discomfort while others may have had more significant reactions requiring medical intervention. For instance, in one severe case, the patient experienced intense redness and itching that led to significant discomfort. This reaction required discontinuation of tacrolimus treatment and the administration of topical corticosteroids to alleviate symptoms. Our results demonstrate a huge safety margin for the

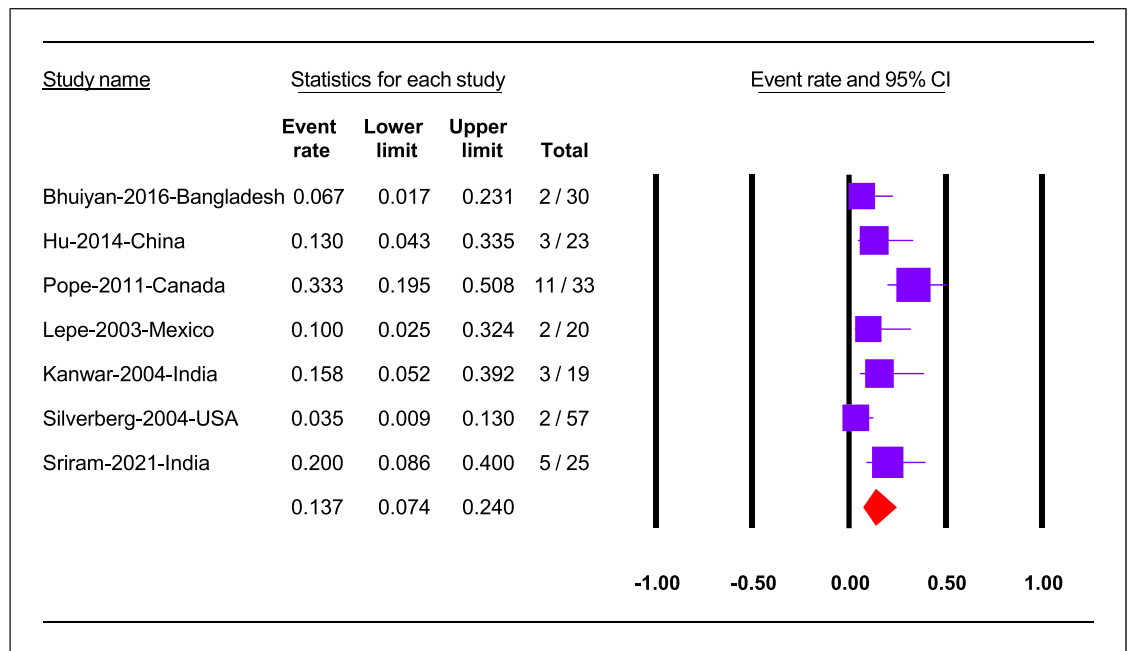


Fig. 7. Overall prevalence of local side effects: the overall prevalence of local side effects from tacrolimus treatment, with 14% (95% CI: 7–24) of patients experiencing local side effects.

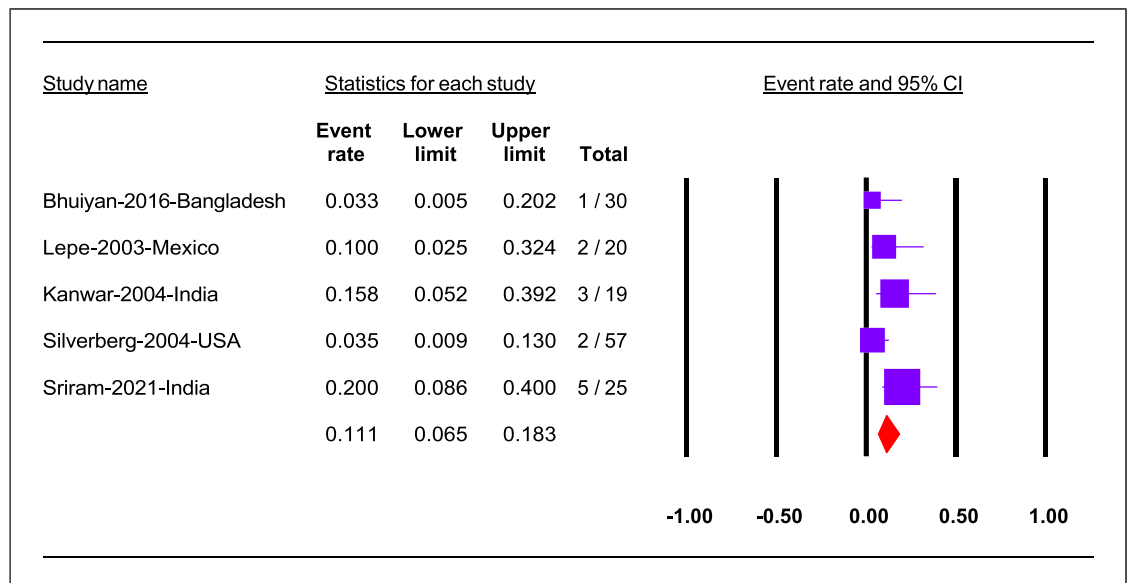


Fig. 8. Prevalence of burning sensation: the prevalence of burning sensation as a side effect, showing that 11% (95% CI: 7–18) of patients experienced this issue.

continuous application of tacrolimus in treating pediatric vitiligo patients.

Tacrolimus affects the immune system by preventing T lymphocytes from becoming active and also has a direct

impact on skin cells. Recently, there have been successful cases where tacrolimus was used alone to treat vitiligo. Comparative studies with strong topical corticosteroids, narrowband ultraviolet B, and psoralen-ultraviolet A have

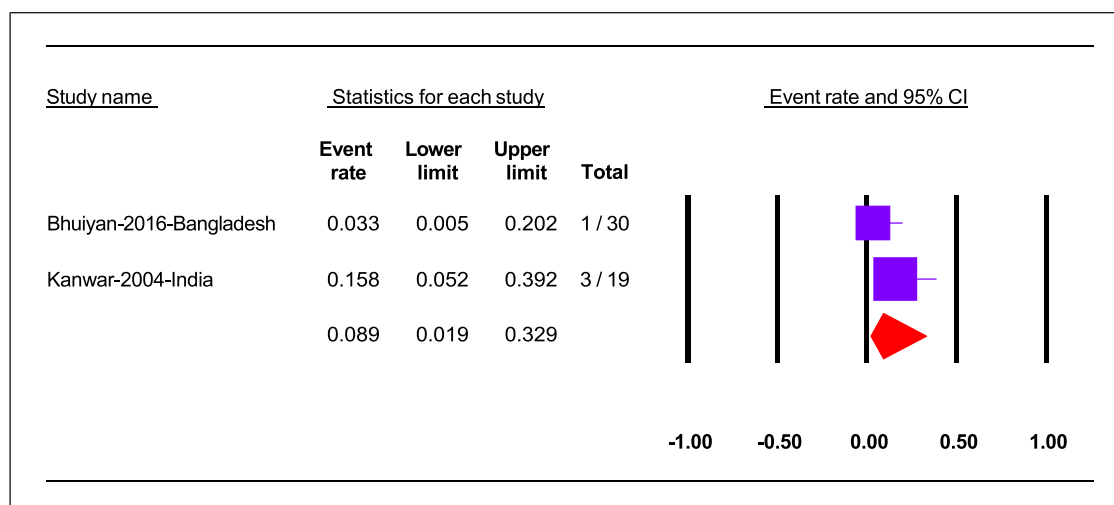


Fig. 9. Prevalence of pruritus: the prevalence of pruritus (itching) as a side effect, indicating that 9% (95% CI: 2–33) of patients reported this condition.

shown that 73%–83.3% of patients experienced some re-pigmentation of their skin lesions [25, 26]. The response rate of 73%–83.3% re-pigmentation refers to the use of strong topical corticosteroids, ultraviolet B, and psoralen-ultraviolet A. Skin thickness alone does not solely determine treatment efficacy; factors such as barrier function, blood flow, pH, moisture levels, and the specific characteristics of the treatment and target tissue all contribute significantly to how effectively treatments work in different areas of the body. Consistent application of the ointment, as recommended, is crucial for achieving optimal results. Topical tacrolimus penetrates the skin at 0.03% and 0.1% strength [27]. Due to a more selective mechanism of action that does not alter collagen synthesis, topical calcineurin inhibitors can be utilized as corticosteroid-sparing agents as they are not associated with agenesis of the skin. This is particularly useful in treating the facial, intertriginous, and genital areas [27]. It is also indicated that tacrolimus is particularly effective for treating the head and neck due to the high concentration of hair follicles in these areas. The duration of the disease also plays a role, with newer lesions typically responding more favorably than older, more established ones.

Regarding the potential dose-response with tacrolimus 0.03% versus 0.1% ointment, the data from our included studies did not indicate a clear dose-response relationship with adverse events. Four out of 8 studies utilized tacrolimus 0.03% twice daily, and three studies used tacrolimus 0.1% twice daily. The overall prevalence of local side effects was comparable between the two concentrations, suggesting that both doses have a similar safety profile in pediatric patients. However, more detailed and larger studies are needed to

conclusively determine if a dose-response relationship exists and to identify any subtle differences in the incidence or severity of adverse events between the two concentrations.

The strengths of this study lie in its comprehensive analysis of tacrolimus's efficacy in treating vitiligo, aligning with previous research findings. The study's emphasis on safety is notable, confirming the absence of systemic adverse effects and reporting only minor localized events, reaffirming tacrolimus's safety profile for continuous application in pediatric cases. The study sheds light on the ongoing discourse among dermatologists regarding combination therapies, highlighting the potential benefit of adjunctive treatments like fractional laser in enhancing efficacy, especially in pediatric patients. However, there are certain limitations of this study. First, we faced significant heterogeneity which was due to differences in the vitiligo site, demographics of patients, and follow-up periods. Second, we did not compare tacrolimus treatment to another treatment arm due to the limited data in this regard. Third, more studies are still needed to assess the safety and efficacy of the addition of another treatment strategy especially laser therapy to tacrolimus in pediatric vitiligo patients.

Conclusion

Tacrolimus exhibited significant efficacy in enhancing re-pigmentation among pediatric vitiligo patients. Notably, it demonstrated a lack of systemic side effects and minimal local adverse reactions, primarily presenting as mild burning sensations and pruritus. However, further studies

are still needed to confirm our findings, assess more outcomes, and ensure the safety and efficacy of tacrolimus if it is added to a proven vitiligo therapy. The study also recommends future studies to investigate the safety and efficacy of tacrolimus ointment in pediatric vitiligo patients should consider the influence of BSA involvement on systemic absorption to provide comprehensive insights. These studies should quantitatively assess BSA involvement using standardized tools and monitor systemic absorption through measures such as blood levels of tacrolimus or its metabolites. Longitudinal follow-up with extended periods can elucidate the impact of BSA involvement on treatment response and safety outcomes over time.

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Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature. Patient consent was not required as this study was based on publicly available data.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.A.A. contributed in analysis and interpretation of data, and reviewed and edited the manuscript. H.A. contributed in writing the manuscript, and reviewed and edited the manuscript. A.A.A. contributed in concept of study, design of the study, and literature review. All authors contributed in final review and approval of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in the manuscript and its online supplementary material. Further inquiries can be directed to the corresponding author.

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