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Short-term (24 weeks) treatment efficacy and safety of ruxolitinib cream in participants with vitiligo: a systematic review and meta-analysis

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Abstract

Importance Vitiligo is a chronic skin disorder causing depigmentation. There is a lack of evidence-based medical evidence regarding ruxolitinib efficacy and safety for vitiligo.

Objective To assess the efficacy and safety of ruxolitinib cream in the treatment of vitiligo.

Methods The databases of PubMed, Embase, and Cochrane Library were searched. The literature screening was independently conducted by two reviewers.

Data extraction and synthesis For continuous variables, weighted mean difference (WMD) along with a 95% confidence interval (CI) was performed. For dichotomous outcomes, we calculated the odds ratios (ORs) or risk ratios (RRs), and their corresponding 95% CIs. The certainty of evidence was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).

Main outcomes and measures Symptoms, quality of life, and safety were evaluated using various measures, including the Facial Vitiligo Area Scoring Index (F-VASI), Total Vitiligo Area Scoring Index (T-VASI), Facial Body Surface Area (F-BAS), Total Body Surface Area (T-BAS) and Treatment-emergent Adverse Events (TEAEs).

Results Three trials, involving a total of 830 participants from nine countries were included (female 388, 46.7%, male 442, 53.3%). The meta-analysis demonstrated a significant increase in the likelihood of participants achieving F-VASI75 (OR, 4.34 [95% CI 2.67–7.06]; high), F-VASI50 (OR 4.71 [95% CI 3.24–6.84]; high), T-VASI75 (OR 2.78 [95% CI 1.10–7.00]; moderate), and T-VASI50 (OR 4.47 [95% CI 2.52–7.92]; high) when compared ruxolitinib to vehicle. Ruxolitinib was associated with more lowered percentage change of F-VASI scores (MD − 32.79 [95% CI − 36.37 to − 29.21]; moderate), and T-VASI scores (MD − 20.22 [95% CI − 23.11 to − 17.33]; moderate) from baseline compared to vehicle. There may not be a significant difference in the occurrence of TEAEs between ruxolitinib and vehicle (RR 1.46 [95% CI 0.85–2.49]; high).

Conclusions The findings suggest that ruxolitinib cream holds promise as a treatment option for vitiligo. Further long-term studies are needed to assess its sustained efficacy and safety profile.

Systematic review registration PROSPERO CRD42023431112.

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Key points

Question Does ruxolitinib cream effectively and safely treat vitiligo?

Findings Three trials, involving a total of 830 participants from nine countries were included (female 388, 46.7%, male 442, 53.3%) in this systematic review. High evidence showed that a significant increase in the likelihood of participants achieving F-VASI75 (OR = 4.34, 95%CI 2.67–7.06), F-VASI50 (OR = 4.71, 95%CI 3.24–6.84), T-VASI75 (OR = 2.78, 95%CI 1.10–7.00), and T-VASI50 (OR = 4.47, 95%CI 2.52–7.92) when compared ruxolitinib to vehicle.

Meaning This study found that ruxolitinib cream holds promise as a treatment option for vitiligo.

Keywords Ruxolitinib, Efficacy, Safety, Systematic review, Meta-analysis

Introduction

Vitiligo is a dermatological condition characterized by the selective loss of melanocytes, resulting in depigmented patches on the skin [1, 2]. Its global prevalence is estimated to be around 0.5–2.0%, affecting individuals of all ages and skin types [3–6]. Despite its impact on quality of life, vitiligo is often underestimated as a cosmetic issue, overshadowing the significant psychological and social burden it imposes [7, 8]. Recognized as an autoimmune disease, vitiligo has witnessed substantial advancements in treatment approaches [9].

Among the emerging therapeutic options, Janus kinase (JAK) inhibitors have demonstrated promising outcomes in managing vitiligo [10]. Ruxolitinib, a potent inhibitor of JAK1 and JAK2, has been investigated in several well-designed clinical trials, presenting evidence of its efficacy in vitiligo patients [10–12]. However, the results of these studies are not completely consistent [10–12], and a comprehensive systematic review and meta-analysis examining the available evidence in this domain is lacking. Systematic reviews and meta-analyses play a pivotal role in evidence-based medical decision-making and the formulation of clinical guidelines [12]. Hence, the primary objective of this study is to assess the short-term (24 weeks) treatment efficacy and safety of ruxolitinib cream in individuals with vitiligo.

Methods

Review methods and registration

The methodology of this systematic review and meta-analysis is based on the Cochrane Handbook [13], and the reporting follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement [14]. The study has been registered on the PROSPERO (CRD42023431112).

Search strategy

A comprehensive search strategy was employed to identify relevant studies for inclusion in this systematic review and meta-analysis. We conducted searches in three major English databases, namely PubMed, Embase, and Cochrane Library, to ensure comprehensive coverage of the literature. In addition, we extended our search to include two clinical trial registration platforms, namely the U.S. ClinicalTrials.gov (https://clinicaltrials.gov/) and the Chinese Clinical Trial Registry (www.chictr.org.cn/index.aspx). The search period spanned from the inception of these databases until April 20, 2023.

To ensure the currency of our findings, we conducted an additional updated search (10 July 2023) to identify any recently published studies that may have emerged since the initial search. Furthermore, to minimize the risk of overlooking relevant studies, we meticulously examined the reference lists of relevant reviews and sought the latest pharmaceutical information in the field.

Eligibility criteria

Prior to the literature screening process, we established specific eligibility criteria in consultation with clinical experts. The eligibility criteria were as follows:

Participants

The study participants had to be diagnosed with vitiligo, with no restrictions on the type of vitiligo or characteristics such as gender, age, or race.

Intervention

The intervention group must have received Ruxolitinib, a specific treatment under investigation. The control group, on the other hand, received the same treatment as the intervention group, except for the administration of ruxolitinib.

Study design

Only randomized controlled trials (RCTs) were considered eligible for inclusion.

We did not impose any restrictions on the language of publication, ensuring that studies from various regions and in different languages were considered.

Study selection

The literature screening was independently conducted by two reviewers in the app Covidence (https://app.covidence.org): first, screening based on titles and abstracts was performed, and conflicts were resolved through discussion. Next, the full texts of the studies included in the previous step were read for final screening, with involvement from a third party to resolve any disagreements. If two or more studies reported the outcomes of the same trial, we combined these studies into a single study. Conversely, if a single study reported the outcomes of two or more trials, we treated each of these trials as separate studies.

Data extraction

Four reviewers divided into two groups participated in the data extraction process. The data extraction into Microsoft Excel included basic information such as study title, authors, publication year, funding, sample size, and intervention details (name, dosage, and administration). We extracted the outcomes of included trials with separate continuous outcomes and dichotomous outcomes. We created a data extraction table in Excel and conducted a pilot test before the formal data extraction. The pilot test ensured that all reviewers had a unified understanding of the extraction criteria and content. Only after achieving consensus among all reviewers, we proceed with the formal data extraction. Data verification and cleaning were carried out by a third reviewer. This approach helps to minimize errors and maintain data quality throughout the process.

Outcomes

Based on the guidance of clinical experts and considering the reported outcomes in the included studies, the following outcomes were assessed (For more detailed information about these outcomes and their descriptions, please see Supplementary Table S1):

Symptoms

The assessment of symptoms involved measuring the percentage change from baseline using various scoring indexes, including F-VASI (Facial Vitiligo Area Scoring Index), T-VASI (Total Vitiligo Area Scoring Index), F-BAS (Facial Body Surface Area), and T-BAS (Total Body Surface Area). Additionally, dichotomous outcomes were considered, such as F-VASI90 (the percentage of participants achieving a $\geq$90% improvement from baseline in F-VASI), F-VASI75, F-VASI50, F-VASI25, T-VASI90 (the percentage of participants achieving a $\geq$90% improvement from baseline in T-VASI), T-VASI75, T-VASI50, T-VASI25, and the percentage of participants achieving a VNS (Vitiligo Noticeability Scale) score of 4 or 5 from baseline.

Quality of life

The assessment of quality of life involved measuring the change from baseline using the Dermatology Life Quality Index (DLQI), with a lower score indicating worse quality of life.

Safety

Safety outcomes included the evaluation of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and discontinuation due to adverse events (AEs).

Risk of bias assessment

Two reviewers, working in pairs and independently, assessed each trial using a modified Cochrane risk of bias tool [15]. The assessment focused on five aspects, including rias arising from the randomization process, bias due to deviations from the intended intervention, bias due to missing outcome data (considered high risk of bias if $\geq$20% missing data), bias in the measurement of the outcome, and bias in the selection of the reported results.

Synthesis analysis

We conducted the meta-analysis using R (version 4.2.0) software. The analysis for continuous variables was performed using the weighted mean difference (WMD) along with a 95% confidence interval (CI). For dichotomous outcomes of symptoms, we calculated the odds ratios (ORs) and their corresponding 95% CIs. For dichotomous outcomes of safety, we calculated the risk ratios (RRs) and their corresponding 95% CIs. To assess the heterogeneity of pooled effect estimates among the included studies, we employed both the chi-squared test and the I^2 statistic. A significance level of $P<0.05$ and an I^2 value greater than 50% were considered indicators of significant heterogeneity. In such cases, a random-effects model was applied. On the other hand, if there was no significant heterogeneity ($P\geq0.05$, $I^2\leq50\%$), a fixed-effect model was used. Subgroup analyses and assessments of publication bias were conducted only when an adequate number of studies were included in the meta-analysis. This approach ensures that the subgroup analyses have sufficient statistical power and that the assessment of publication bias is reliable. Microsoft Excel was used to organize data during analysis.

Assessing certainty of evidence

The certainty of evidence was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework [16]. This framework

categorizes evidence into four levels of certainty: high, moderate, low, or very low. For randomized controlled trials (RCTs), the initial rating for certainty starts at high, but it could be rated down based on limitations due to the risk of bias [17], imprecision [18], inconsistency (heterogeneity) [19], indirectness [20], and publication bias [21].

Results

Included studies

A systematic search was conducted, resulting in the identification of 217 records from multiple databases. Additionally, 293 records were obtained from trial registration sources. After removing duplicate records and screening the titles and abstracts, a total of 117 records were excluded based on predetermined criteria. Subsequently, the full-text articles of the remaining records underwent a thorough assessment, ultimately leading to the inclusion of three trials reported in two studies for the meta-analysis (Fig. 1).

Study characteristics

Three trials, involving a total of 830 participants with vitiligo from nine countries, were included in the analysis. Detailed inclusion and exclusion criteria for patient selection can be found in Supplementary Table S2. Table 1 and Supplementary Table S3 provide a summary of the characteristics of the included trials. Of the participants, 388 (46.7%) were female, while 442 (53.3%) were male, with the mean age ranging from 38.9 to 48.3 years and the mean duration of vitiligo ranging from 9.7 to 15.9 years. Among the participants, 11 (1.3%) had segmental vitiligo, while the remaining 819 (98.7%) had non-segmental vitiligo. The treatment interventions included the use of a vehicle and four different doses of topical ruxolitinib cream: 0.15% (once a day), 0.5% (once a day), 1.5% (once a day), and 1.5% (twice a day).

Risk of bias assessment

The risk of bias assessment for each domain and the overall level can be found in Supplementary Table S4. Notably, for every outcome reported in the three trials, the risk of bias was determined to be "low."

Findings on symptoms

F-VASI90, F-VASI75, F-VASI50, and F-VASI25

Three trials, involving a total of 830 patients, were included in the meta-analysis to assess the effectiveness of ruxolitinib compared to the vehicle by F-VASI90, F-VASI75, F-VASI50, and F-VASI25. The meta-analysis demonstrated a significant increase in the likelihood of participants achieving F-VASI90

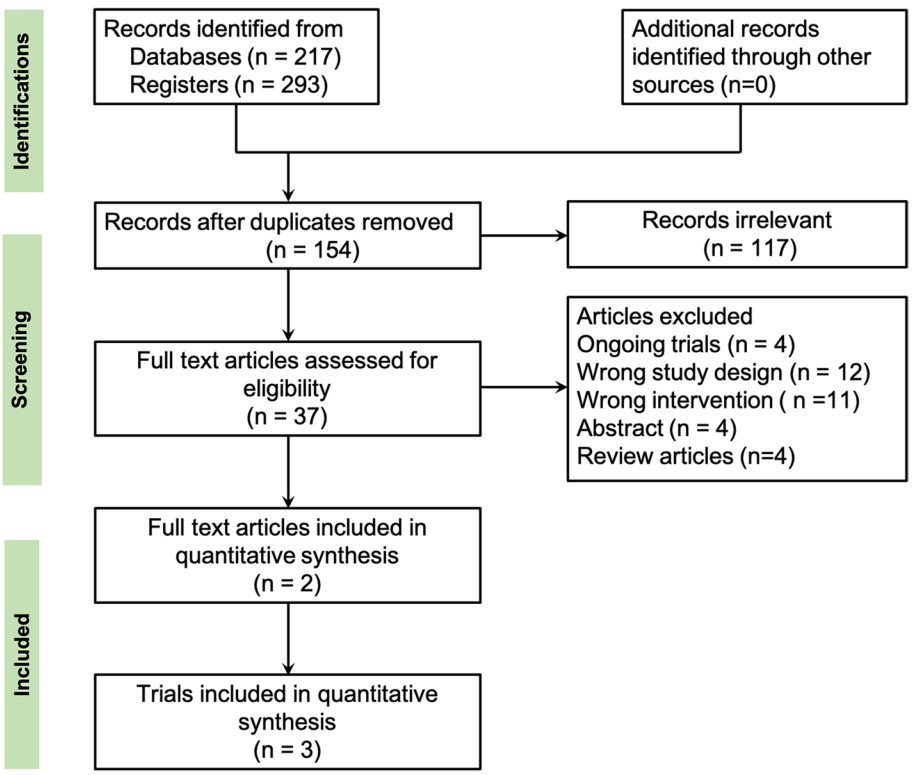

Fig. 1 Flow diagram of article selection for the meta-analysis

Table 1 List of included trials and baseline characteristics

Study	Country	Sample sizes	Proportion of males, %	Proportion of females, %	Age, mean (SD), years	Intervention (sample sizes)	Control (sample sizes)	Duration of vitiligo, mean (SD), y	Type of vitiligo	F-VASI scores, mean (SD)	F-BSA scores, mean (SD)	Funding
Rosmarin 2020	USA	157	73, 46.5%	84, 53.5%	48.3 (12.9)	Topical Ruxolitinib cream (0.15%), qd, 24 weeks (31) Topical Ruxolitinib cream (0.50%), qd, 24 weeks (31) Topical ruxolitinib cream (1.50%), qd, 24 weeks (30) Topical ruxolitinib cream (1.50%), bid, 24 weeks (33)	Vehicle cream (32)	9.7 (6.6)	Segmental (11), non-Segmental (146)	1.3 (0.8)	1.5 (0.9)	Incyte
Rosmarin 2022 (TRuE-V1)	USA, Canada, Bulgaria, France, Germany, Italy, the Netherlands, Poland, Spain	330	144, 43.6%	186, 56.3%	40.2 (15.9)	Topical ruxolitinib cream (1.50%), qd, 24 weeks (221)	Vehicle cream (109)	13.6 (11.1)	Segmental (0), non-segmental (330)	1.0 (0.6)	1.1 (0.7)	Incyte
Rosmarin 2022 (TRuE-V2)	USA, Canada, Bulgaria, France, Germany, Italy, the Netherlands, Poland, Spain	343	171, 49.9%	172, 50.1%	38.9 (14.3)	Topical ruxolitinib cream (1.50%), qd, 24 weeks (228)	Vehicle cream (115)	15.9 (11.9)	Segmental (0), non-segmental (343)	0.9 (0.5)	1.0 (0.6)	Incyte

(OR 9.61 [95% CI 3.67–25.19]; $I^2 = 0\%$; GRADE assessment: moderate certainty), F-VASI75 (OR 4.34 [95% CI 2.67–7.06]; $I^2 = 0\%$; GRADE assessment: high certainty), F-VASI50 (OR 4.71 [95% CI 3.24–6.84]; $I^2 = 0\%$; GRADE assessment: high certainty), and F-VASI25 (OR 4.74 [95% CI 3.28–6.86]; $I^2 = 35\%$; GRADE assessment: high certainty) when compared ruxolitinib to vehicle (Fig. 2; Table 2).

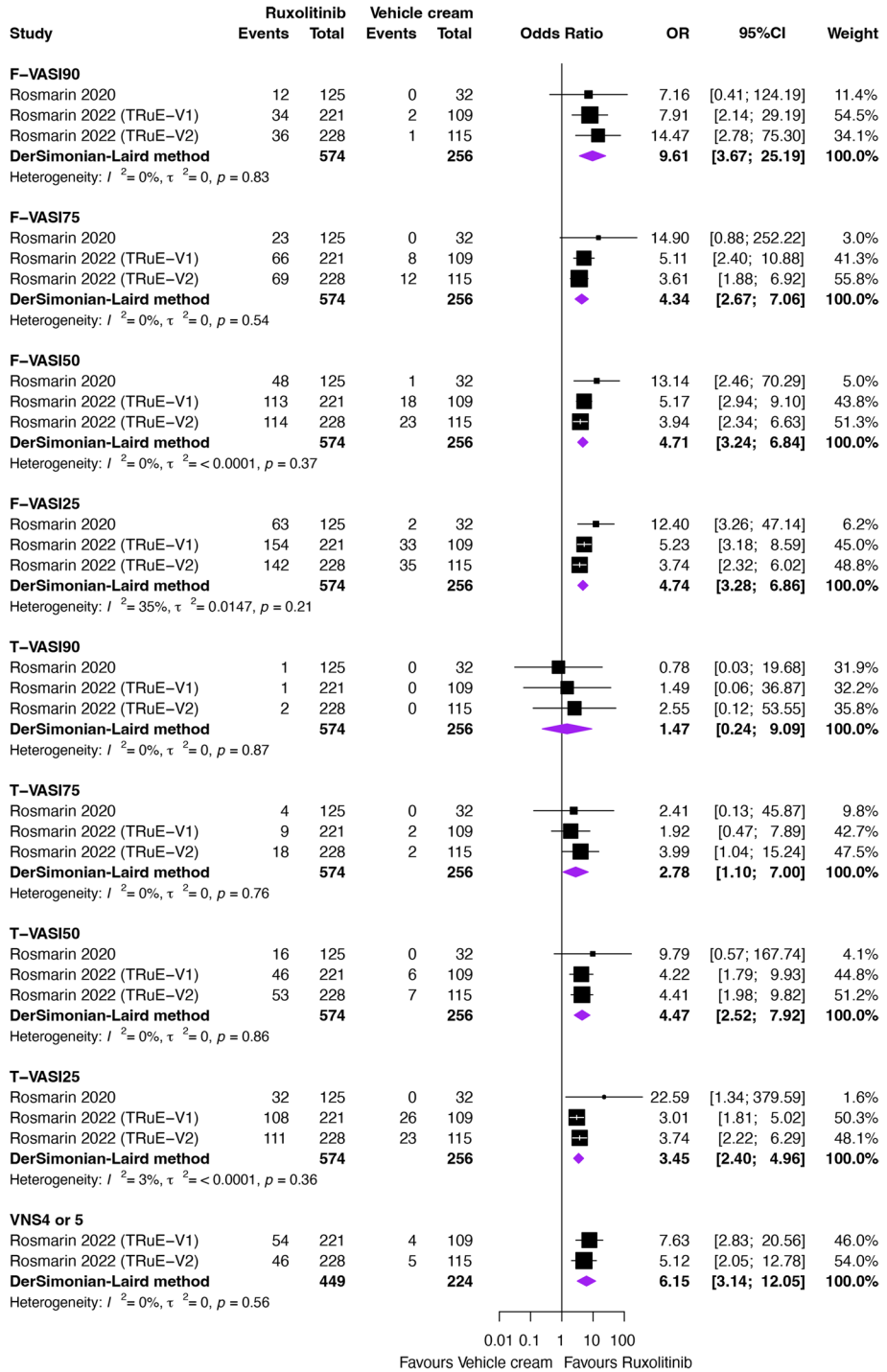

Fig. 2 Ruxolitinib vs vehicle cream on F-VASI90, F-VASI75, F-VASI50, F-VASI25, T-VASI90, T-VASI75, T-VASI50, T-VASI25 and VNS-4 or 5

Table 2 GRADE summary of findings for ruxolitinib versus vehicle cream treatment for vitiligo

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		Vehicle cream	Ruxolitinib Cream		
Percentage of participants achieving F-VASI90	Odds ratio: 9.61 (CI 95% 3.67 - 25.19) Based on data from 830 participants in 3 studies Follow up 24 weeks	**12** per 1000 Difference: **93 more per 1000** (CI 95% 31 more - 222 more)	**105** per 1000	**Moderate** Due to serious imprecision[a]	Ruxolitinib cream probably improves percentage of participants achieving F-VASI90
Percentage of participants achieving F-VASI75	Odds ratio: 4.34 (CI 95% 2.67 - 7.06) Based on data from 30 participants in 3 studies Follow up 24 weeks	**78** per 1000 Difference: **191 more per 1000** (CI 95% 106 more - 296 more)	**269** per 1000	**High**	Ruxolitinib cream improves percentage of participants achieving F-VASI75
Percentage of participants achieving F-VASI50	Odds ratio: 4.71 CI 95% 3.24 - 6.81) Based on data from 830 participants in 3 studies Follow up 24 weeks	**164** per 1000 Difference: **316 more per 1000** (CI 95% 225 more - 408 more)	**480** per 1000	**High**	Ruxolitinib cream improves percentage of participants achieving F-VASI50
Percentage of participants achieving F-VASI25	Odds ratio: 4.74 (CI 95% 3.28 - 6.86) Based on data from 830 participants in 3 studies Follow up 24 weeks	**273** per 1000 Difference: **367 more per 1000** (CI 95% 279 more - 447 more)	**640** per 1000	**High**	Ruxolitinib cream improves percentage of participants achieving F-VASI25
Percentage of participants achieving T-VASI90	Odds ratio: 1.47 (CI 95% 0.24 - 9.09) Based on data from 830 participants in 3 studies Follow up 24 weeks	**6** per 1000 Difference: **3 more per 1000** (CI 95% 5 fewer - 46 more)	**9** per 1000	**Moderate** Due to serious imprecision[a]	Ruxolitinib cream probably improves percentage of participants achieving T-VASI90
Percentage of participants achieving T-VASI75	Odds ratio: 2.78 (CI 95% 1.1 - 7.0) Based on data from 830 participants in 3 studies Follow up 24 weeks	**16** per 1000 Difference: **27 more per 1000** (CI 95% 2 more - 86 more)	**43** per 1000	**Moderate** Due to serious imprecision[a]	Ruxolitinib cream probably improves percentage of participants achieving T-VASI75
Percentage of participants achieving T-VASI50	Odds ratio: 4.47 (CI 95% 2.52 - 7.92) Based on data from 830 participants in 3 studies Follow up 24 weeks	**51** per 1000 Difference: **143 more per 1000** (CI 95% 68 more - 248 more)	**194** per 1000	**High**	Ruxolitinib cream improves percentage of participants achieving T-VASI50
Percentage of participants achieving T-VASI25	Odds ratio: 3.45 (CI 95% 2.4 - 4.96) Based on data from 830 participants in 3 studies Follow up 24 weeks	**191** per 1000 Difference: **258 more per 1000** (CI 95% 171 more - 348 more)	**449** per 1000	**High**	Ruxolitinib cream improves percentage of participants achieving T-VASI25
Percentage of participants achieving VNS4 or 5	Odds ratio: 6.15 (CI 95% 3.14 - 12.05) Based on data from 673 participants in 2 studies Follow up 24 weeks	**40** per 1000 Difference: **164 more per 1000** (CI 95% 76 more - 294 more)	**204** per 1000	**Moderate** Due to serious imprecision[a]	Ruxolitinib cream probably improves percentage of participants achieving VNS4 or 5

Table 2 (continued)

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		Vehicle cream	Ruxolitinib Cream		
Treatment-related adverse events	Relative risk: 1.46 (CI 95% 0.85 - 2.49) Based on data from 830 participants in 3 studies Follow up 24 weeks	**109** per 1000 Difference: **50 more per 1000** (CI 95% 16 fewer - 162 more)	**159** per 1000	**High**	Ruxolitinib cream has little or no difference on treatment-related adverse events
Serious adverse events	Relative risk: 2.25 (CI 95% 0.59 - 8.67) Based on data from 830 participants in 3 studies Follow up 24 weeks	**4** per 1000 Difference: **5 more per 1000** (CI 95% 2 fewer - 31 more)	**9** per 1000	**Moderate** Due to serious imprecision[a]	Ruxolitinib cream probably has little or no difference on serious adverse events
Adverse events leading to discontinuation	Relative risk: 0.38 (CI 95% 0.1 - 1.48) Based on data from 830 participants in 3 studies Follow up 24 weeks	**12** per 1000 Difference: **7 fewer per 1000** (CI 95% 11 fewer - 6 more)	**5** per 1000	**High**	Ruxolitinib cream has more or no difference on adverse events leading to discontinuation
Percentage change from baseline F-VASI scores	Measured by: Scale: - Lower better Based on data from 830 participants in 3 studies Follow up 24 weeks	**-15.8** Mean Difference: **MD 32.79 lower** (CI 95% 36.37 lower - 29.21 lower)	**-48.59** Mean	**Moderate** Due to serious inconsistency[b]	Ruxolitinib cream probably decreases percentage change from baseline F-VASI scores
Percentage change from baseline T-VASI scores	Measured by: Scale: - Lower better Based on data from 830 participants in 3 studies Follow up 24 weeks	**-8.99** Mean Difference: **MD 20.22 lower** (CI 95% 23.11 lower - 17.33 lower)	**-29.21** Mean	**Moderate** Due to serious inconsistency[c]	Ruxolitinib cream probably decreases percentage change from baseline T-VASI scores
Percentage change from baseline F-BSA scores	Measured by: Scale: - Lower better Based on data from 673 participants in 2 studies Follow up 24 weeks	**-8.25** Mean Difference: **MD 19.4 lower** (CI 95% 19.91 lower - 18.89 lower)	**-27.65** Mean	**High**	Ruxolitinib cream decreases percentage change from baseline F-BSA scores
Percentage change from baseline T-BSA scores	Measured by: Scale: - Lower better Based on data from 673 participants in 2 studies Follow up 24 weeks	**-3.15** Mean Difference: **MD 10.5 lower** (CI 95% 13.34 lower - 7.67 lower)	**-13.65** Mean	**High**	Ruxolitinib cream decreases percentage change from baseline T-BSA scores
Change from baseline DLQI scores	Measured by: Scale: - Lower better Based on data from 673 participants in 2 studies Follow up 24 weeks	**0.72** Mean Difference: **MD 0.46 lower** (CI 95% 0.73 lower - 0.19 lower)	**-1.18** Mean	**Moderate** Due to serious inconsistency[d]	Ruxolitinib cream probably decreases change from baseline DLQI scores slightly

[a] Rated down 1 level for serious imprecision due to wide confidence intervals

[b] Rated down 1 level for serious inconsistency: serious due to statistical (I^2=97%)

[c] Rated down 1 level for serious inconsistency: serious due to statistical (I^2=98%)

[d] Rated down 1 level for serious inconsistency: serious due to statistical (I^2=95%).

T-VASI90, T-VASI75, T-VASI50, and T-VASI25

Three trials, involving a total of 830 patients, were included in the meta-analysis to assess the effectiveness of ruxolitinib compared to the vehicle by T-VASI90, T-VASI75, T-VASI50, and T-VASI25. The meta-analysis results demonstrated that the use of ruxolitinib did not significantly increase the likelihood of participants achieving T-VASI90 compared to vehicle (OR 1.47 [95% CI 0.24–9.09]; $I^2=0\%$; GRADE assessment: moderate certainty). The meta-analysis demonstrated a significant increase in the likelihood of participants achieving T-VASI75 (OR 2.78 [95% CI 1.10–7.00]; $I^2=0\%$; GRADE assessment: moderate certainty), T-VASI50 (OR 4.47 [95% CI 2.52–7.92]; $I^2=0\%$; GRADE assessment: high certainty), and T-VASI25 (OR 3.45 [95% CI 2.40–4.96]; $I^2=3\%$; GRADE assessment: high certainty) when compared ruxolitinib to vehicle (Fig. 2; Table 2).

VNS-4 or 5

The meta-analysis of two trials, involving a total of 673 patients, demonstrated that the use of ruxolitinib led to a higher proportion of participants achieving VNS-4 or 5 (OR 6.15 [95% CI 3.14–12.05]; $I^2=0\%$; GRADE assessment: moderate certainty) in comparison to vehicle (Fig. 2; Table 2).

F-VASI and T-VASI

Three trials, which included 830 patients, reported the outcome of percentage change from baseline of F-VASI scores. The results showed that ruxolitinib was associated with more lowered percentage change of F-VASI scores from baseline (MD − 32.79 [95% CI − 36.37 to − 29.21]; $I^2=97\%$; GRADE assessment: moderate certainty) compared to vehicle. Three trials, which included 830 patients, reported the outcome of percentage change from baseline of T-VASI scores. The results showed that ruxolitinib was associated with more lowered percentage change of T-VASI scores from baseline (MD − 20.22 [95% CI − 23.11 to − 17.33]; $I^2=98\%$; GRADE assessment: moderate certainty) compared to vehicle (Fig. 3; Table 2).

F-BSA and T-BSA

Two trials, which included 673 patients, reported the outcome of percentage change from the baseline of F-BSA scores. The results showed that ruxolitinib was associated with more lowered percentage change of F-BSA scores from baseline (MD − 19.40 [95% CI − 19.91 to − 18.89]; $I^2=0\%$; GRADE assessment: high certainty) compared to vehicle. Two trials, which included 673 patients, reported the outcome of percentage change from baseline of T-BSA scores. The results showed that ruxolitinib was associated with more lowered percentage

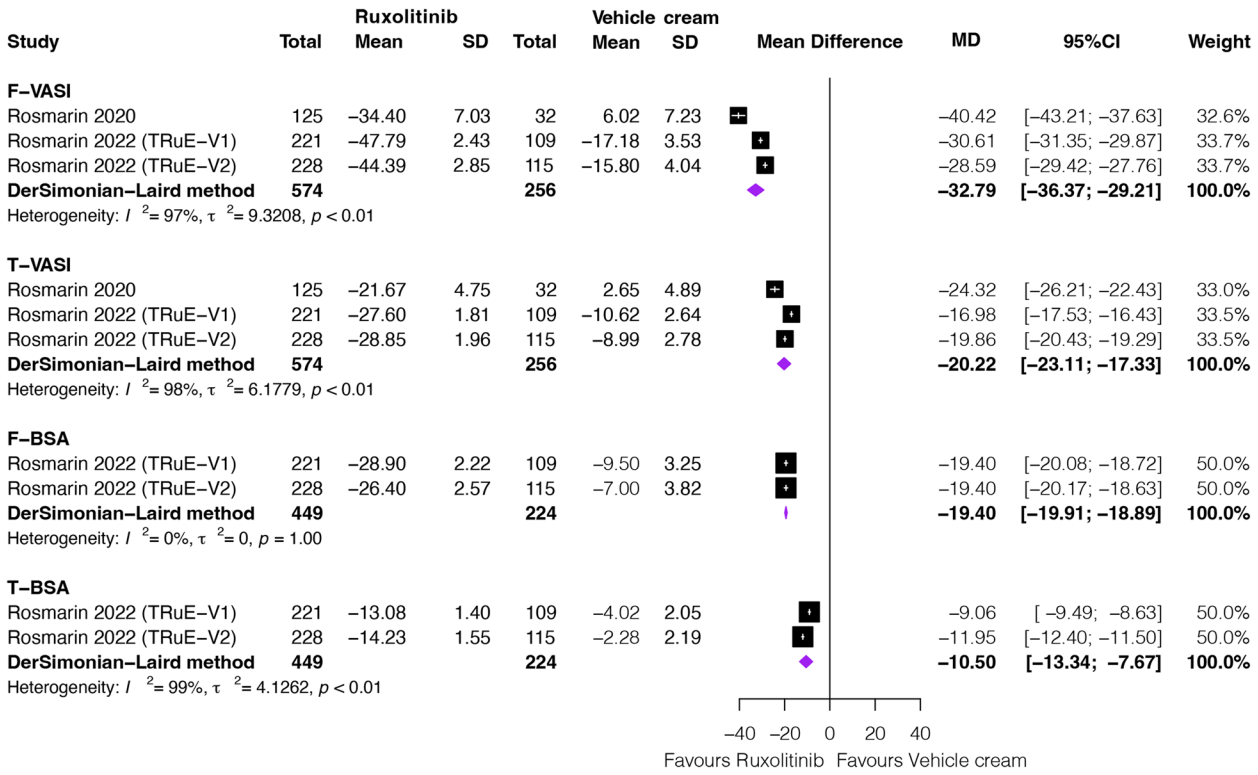

Fig. 3 Ruxolitinib vs vehicle cream on F-VASI, T-VASI, F-BSA, and T-BSA

change of T-BSA scores from baseline (MD − 10.50 [95% CI, − 13.34 to − 7.67]; I^2 = 99%; GRADE assessment: high certainty) compared to vehicle (Fig. 3; Table 2).

Findings on quality of life

Two trials, which included 673 patients, reported the outcome of change from baseline DLQI scores. The results showed that ruxolitinib was associated with more lowered change of DLQI scores from baseline (MD − 0.46 [95% CI − 0.73 to − 0.19]; I^2 = 95%; GRADE assessment: moderate certainty) compared to vehicle (Supplementary Figure S1; Table 2).

Findings on safety

Three trials, which included 830 patients, reported these outcomes of TEAEs, SAEs, and discontinuation due to AEs. The meta-analysis results indicated that there may not be a significant difference in the occurrence of TEAEs (RR 1.46 [95% CI 0.85–2.49]; I^2 = 53%; GRADE assessment: high certainty), SAEs (RR 2.25 [95% CI 0.59–8.67]; I^2 = 0%; GRADE assessment: moderate certainty), and discontinuation due to AEs (RR 0.38 [95% CI 0.10–1.48]; I^2 = 0%; GRADE assessment: high certainty) between ruxolitinib and vehicle (Supplementary Figure S5; Table 2).

Another analyses

Subgroup analyses and assessments of publication bias were not conducted due to the limited number of clinical trials included in the analysis (only three trials) and the fact that all trials were conducted by the same research group, performing subgroup analyses and assessing publication bias may not be appropriate or informative.

Discussion

In patients with vitiligo, we found moderate-certainly or high-certainly evidence that ruxolitinib cream improves clinical symptoms compared to vehicle cream, particularly in reducing facial vitiligo. Although there is moderate-quality evidence that ruxolitinib cream improves the quality of life in vitiligo patients compared to vehicle cream, the observed mean decrease of 0.46 scores was not practically significant in relation to a total score of 30. Current evidence supports the safety of ruxolitinib as a topical treatment for vitiligo.

This systematic review and meta-analysis have several notable strengths. These include a comprehensive search strategy to identify eligible trials, independent assessment of study selection, data extraction, and risk of bias by two reviewers, and the application of the GRADE approach to evaluate the certainty of evidence. Furthermore, the presentation of absolute effect measures enhances the interpretability of the findings, facilitating a more meaningful understanding of the clinical implications.

Limitations of this systematic review and meta-analysis are as follows: (1) all three trials were conducted by the same research group introduces potential bias and may impact the reliability of the results, but this also reduces inherent heterogeneity among the trials; (2) despite the inclusion of large sample sizes, the limited number of trials results in wider CIs for certain outcomes, which lowers the level of certainty in the evidence; (3) all participants were from Europe and America, so it remains to be determined whether the findings of our study are applicable to patients of Asian and African; (4) due to the limited number of trials, subgroup analyses predefined by clinical experts, different doses of ruxolitinib, could not be done; (5) the findings of our study are based on short-term treatment (24 weeks) with ruxolitinib, and the long-term efficacy and safety of ruxolitinib are currently unknown. Future trials should ideally address these issues, and it is necessary to update this study timely.

Vitiligo is categorized into three distinct forms based on the distribution of skin lesions: non-segmental, segmental, and mixed vitiligo [22]. Non-segmental vitiligo is the most common form. The symmetrical nature of the white patches is a distinguishing feature of non-segmental vitiligo, differentiating it from other forms of the condition [2]. Non-segmental vitiligo and segmental vitiligo are believed to have distinct pathogenetic mechanisms due to their differing clinical patterns. However, recent data suggest that there may be overlapping inflammatory mechanisms involved in both segmental and non-segmental vitiligo that contribute to the development of both subtypes [23]. In our study, the majority (98.7%) of the vitiligo cases included were non-segmental vitiligo. Therefore, clinicians should carefully consider the evidence provided by this study when making treatment decisions for different subtypes of vitiligo. Future trials should be conducted to specifically investigate the efficacy of ruxolitinib in each subtype of vitiligo that can gain a clearer understanding of the treatment's efficacy and applicability in diverse patient populations.

Currently, there are many treatment options for vitiligo, and in many clinical situations, combination therapy needs to be considered [24]. The majority of participants included in our study had a history of prior therapy, including topical corticosteroids, calcineurin inhibitors, phototherapy, and photochemotherapy, indicating that they were not first-episode patients. Indeed, the effectiveness of ruxolitinib specifically for first-episode vitiligo patients and the potential benefits of combining it with other treatments require further investigation [25, 26]. Conducting future trials based on these hypotheses would provide valuable insights into the comparative efficacy of ruxolitinib in different patient populations and the potential synergistic

effects of combination therapies that will contribute to advancing our understanding of the optimal treatment strategies for vitiligo.

The skin plays a central role in various aspects of life. Many patients with vitiligo experience elevated levels of stress and often face social stigma due to their visible skin depigmentation [27–29]. In addition to the effectiveness of the treatment, various factors can contribute to the overall quality of life of patients with vitiligo, such as age at onset, extent, distribution, stigma, self-esteem, and self-concept. Therefore, the lack of practically significant improvement observed in our study does not show that ruxolitinib is incapable of improving the quality of life in individuals with vitiligo. Indeed, the duration of treatment and the follow-up period can also significantly impact the assessment of quality of life outcomes in patients with vitiligo. The short-term nature of the treatment duration in the current study (24 weeks) may not have been sufficient to capture the full potential of ruxolitinib in improving quality of life. Additionally, long-term follow-up is necessary to evaluate the sustained effects of the treatment on patients' well-being over time. It is plausible that extended treatment duration and longer follow-up periods could yield different results and potentially demonstrate a positive impact of ruxolitinib on the quality of life of individuals with vitiligo. Similarly, the safety assessment of ruxolitinib in the treatment of vitiligo would benefit from studies with longer follow-up periods and larger sample sizes.

To our knowledge, this systematic review and meta-analysis is the first to evaluate the efficacy and safety of ruxolitinib for patients with vitiligo. Unlike previous reviews [9, 30–33], our study has several distinct features. Firstly, it exclusively incorporates evidence from randomized controlled trials. Secondly, we employed the GRADE approach to evaluate the certainty of the evidence, providing a comprehensive and standardized assessment of the quality of the included studies. Lastly, to facilitate interpretation, we presented the absolute effects of ruxolitinib treatment.

Conclusion

The results of our study provide compelling evidence for the efficacy of ruxolitinib in the short-term treatment of vitiligo. These findings indicate that ruxolitinib cream has the potential to be a promising treatment option for vitiligo. However, it is important to note that further study is necessary to evaluate the sustained efficacy and safety of ruxolitinib over a longer duration. Long-term and larger sample size studies are crucial in determining the prolonged effects and safety profile of ruxolitinib in the treatment of vitiligo.

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
YY, XLS, and YTZ planned and designed the study. YY and LZ developed search strategies. YY, LZ, SHY, and XTG screened potential studies and extracted data from the included studies. YY and YTZ managed the data and performed the statistical analysis. XLS conducted the arbitration under disagreement and ensured that there were no errors. XLS and YTZ provided methodological support and helped to interpret findings. YY wrote the first draft. XLS and YTZ revised the draft. All authors read and approved the final version of the manuscript.

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Availability of data and materials
Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. Data are available upon reasonable request from the corresponding author.

Declarations

Ethics approval and consent to participate
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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