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ORIGINAL PAPER

The effects of tacrolimus plus phototherapy in the treatment of vitiligo: a meta-analysis

Yujie Dong[1] · Qi Yang[2] · Baofeng Guo[3] · Jiajing Zhu[4] · Xiaojie Sun[5]

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Abstract

The objective of this meta-analysis was performed to compare the effects of tacrolimus plus phototherapy in the treatment of patients with vitiligo. Relevant studies were identified by searching PubMed, Embase, and Web of Science databases. The main outcomes of interest included excellent response (≥ 75% repigmentation), good response (50–75% repigmentation), moderate response (25%–50% repigmentation), and poor response (< 25% repigmentation). Risk ratio (RR) with 95% confidence intervals (95% CIs) was used to calculate the data. Eleven studies were included in this study. Compared with phototherapy alone, combination treatment of tacrolimus and phototherapy significantly improved excellent response rate (RR = 1.40, 95% CI 1.16, 1.69; $P < 0.001$) and reduced the poor response rate (RR = 0.37, 95% CI 0.22, 0.61; $P = 0.001$). However, the good response rate (RR = 1.00, 95% CI 0.59, 1.69, $P = 1.000$) and moderate response rate (RR = 0.91, 95% CI 0.60, 1.38; $P = 0.653$) were not significantly different between the two treatments. Subgroup analysis suggested that combination treatment had a higher excellent response rate than phototherapy alone for lesions located in the face and proximal limbs. Both NB-UVB and EL, when added to tacrolimus, resulted in a significantly higher excellent response rate than they were used alone. Meta-regression analysis showed that age was a predictive factor that influenced the effect of combination treatment on an excellent response, in which children had a high excellent response to the treatment. Other demographic and clinical variables, including gender, disease duration, family history, and type of vitiligo, did not have any impact on the treatment effect. Combination treatment with tacrolimus and phototherapy was more effective than phototherapy monotherapy for patients with vitiligo, especially in the lesions located in the face and proximal limbs. More large-scale, well-performed trials are needed to verify our findings.

Keywords Tacrolimus · Phototherapy · Vitiligo · Meta-analysis

Introduction

Vitiligo is an acquired and progressive depigmentary disorder characterized by the absence of functional melanocytes in skin and hair follicles [1]. Vitiligo affects 1% of the population in the world [2], and its prevalence has been as high as 4% in some South Asian, Mexican, and American populations [3]. Vitiligo might begin at any age, but half of the patients are known to occur from the second or third decades of life [4]. Vitiligo is a chronic disease, which is not only associated with the appearance of patients, but also with the psychological trauma that affects social activity and self-esteem [5]. These theories, which attempt to explain the cause of vitiligo, include genetic predisposition, autoimmunity, neural, biochemical, oxidative stress, viral infection, and melanocyte detachment [6–10]. Among the therapies, phototherapy is a mainstay of vitiligo treatment

✉ Xiaojie Sun
sunxj@jlu.edu.cn

1 Department of Emergency, China-Japan Union Hospital of Jilin University, Changchun 130033, China

2 Department of Obstetrics and Gynecology, China-Japan Union Hospital of Jilin University, Changchun 130033, China

3 Department of Plastic and Reconstruction Surgery, China-Japan Union Hospital of Jilin University, Changchun 130033, China

4 Radiology Department, China-Japan Union Hospital of Jilin University, Changchun 130033, China

5 Department of Plastic and Reconstruction Surgery, China-Japan Union Hospital of Jilin University, No. 126 Xiantai Street, Changchun 130033, China

with different efficacy rates. Narrowband ultraviolet B (NB-UVB) is regarded as the "gold standard" for diffuse vitiligo due to its simplicity, safety, and efficacy [11]. Excimer laser/light (EL) was approved by the US Food and Drug Administration for the treatment of vitiligo [12], and it emits monochromatic light of 308 nm, which produces photobiological effects similar to those of NB-UVB [13]. Topical immunomodulators (tacrolimus, pimecrolimus) are regarded as effective and safe agents for long-term use in vitiligo, since they are not associated with skin atrophy [2]. A previous study reported that tacrolimus leads to a repigmentation rate of 75% or more in 61% of patients when used alone [14]. Another study showed that a repigmentation rate of 50% or more turned to be 73% when tacrolimus was added to the treatment of NB-UVB [1].

Therefore, we conducted this meta-analysis to compare the efficacy of tacrolimus plus phototherapy with phototherapy alone in the treatment of patients with vitiligo.

Materials and methods

Literature search

We performed this meta-analysis following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [15] and reported it in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [16]. A comprehensive literature search of PubMed, Embase, and Web of Science database was carried out on February 24, 2020. The search terms were listed as the followings: ("vitiligo" [MeSH Terms] OR "vitiligo" [All Fields]) AND ("tacrolimus" [MeSH Terms] OR "tacrolimus" [All Fields]) AND (("phototherapy" [MeSH Terms] OR "phototherapy" [All Fields]) OR excimer [All Fields] OR ("lasers" [MeSH Terms] OR "lasers" [All Fields] OR "laser" [All Fields]) OR ultraviolet [All Fields] OR UVB [All Fields]).

Study selection

Studies were included in this meta-analysis if they provided relevant information regarding the PICOS approach [17]. The following inclusive criteria were applied: (1) population: adults or children who were diagnosed with vitiligo; (2) intervention: combination treatment of tacrolimus and EI or NB-UVB; (3) control: tacrolimus, EI, NB-UVB, or other treatments; (4) outcomes: excellent response (≥ 75% repigmentation of each designed patch or whole lesion in a patient), good response (50–75% repigmentation), moderate response (25%–50% repigmentation) and poor response (< 25% repigmentation); (5) study design: randomized controlled trial (RCT), or comparative trial, or open-label trials; (6) sample size: more than ten subjects or patches in each group; (7) treatment duration: more than 12 weeks or 24 sessions of phototherapy therapy.

Data extraction

We used a standardized data-extraction sheet to extract the following data from each study: first author, year of publication, number of patients in each group, country, patients' baseline characteristics (age, gender, duration of disease, age at the onset of a lesion, sites affected, skin type, family history of vitiligo) and outcome data. Any discrepancies between the investigators were resolved by discussion and consensus.

Risk of bias assessment

The Cochrane risk-of-bias tool was used to assess the risk of bias in an RCT [18]. This method consists of seven items, including random sequence generation, allocation concealment; blinding of outcome participants and personnel; blinding of outcome assessment; incomplete outcome data, selective reporting, and other bias [18]. Each RCT was classified as being at low, high, or unclear risk of bias based on the criteria mentioned above.

Statistical analysis

We calculated the risk ratio (RR) with a 95% confidence interval (95% CI) for dichotomous outcomes. Before data were synthesized, a heterogeneity test was performed using Cochrane Q and I^2 statistic, in which $P < 0.1$ or $I^2 > 50\%$ were considered to be significant [19]. When significant heterogeneity was identified, a random-effects model was used to pool the results [20]; otherwise, a fixed-effects model was applied [21]. We carried out a sensitivity analysis to investigate the influence of excluding any single trial on the overall estimate. Publication bias was assessed by Begg's [22] and Egger's test [23]. P value less than 0.05 was judged as statistically significant. All statistical analyses were performed using STATA, version 12.0 (Stata Corporation, College Station, TX, USA).

Meta-regression

We also performed meta-regression to explore whether the overall estimate was influenced by the demographic (age, gender) and clinical variables (disease duration, family history, and type of vitiligo). In this regression model, the level of repigmentation was defined as the dependent variable (y), and the covariates mentioned above were used as independent variables (χ).

Results

Selection of studies

A total of 587 publications were obtained from an electronic search of the databases, of which 364 were excluded because of duplicate records. Upon review of title and abstracts, leaving 16 publications for full-text information review. However, 5 of them were excluded because 2 used other topical agents rather than tacrolimus, two provided data that were unavailable for analysis, and one was a single-arm trial. Finally, 11 studies [14, 24–33] that met the inclusion criteria were included in this meta-analysis (Fig. 1).

Study characteristics

The baseline characteristics of the included studies are presented in Table 1. Among the included studies, 8 were performed with RCT design (including 5 intra-individual study) [24, 25, 27, 29–33], and 3 were comparative studies [14, 26, 28]. Three studies were conducted in India [26, 29, 31], two in Pakistan [24, 25], and Italy [14, 33], respectively, and each one in France [27], Turkey [28], and Thailand [30]. The sample size ranged greatly, which ranged from 8 to 159, with a total of 588 patients. Ten of eleven studies targeted adults [14, 24, 25, 27–33] and the remaining one targeted children [26]. The type of NB-UVB was used in seven studies [14, 24–26, 29–31], and EL in four studies [27, 28, 32, 33].

Risk of bias assessment

The details of the risk of bias assessment in RCTs are shown in Fig. 2. Overall, three RCTs [24, 27, 32] were recognized as being at low risk of bias, two [25, 33] at unclear risk of bias, and three [29–31] at high risk of bias. The reasons for three RCTs at high risk of bias were that they did not perform blind to the participants or outcome assessors. The reasons for two RCTs at unclear risk of bias were that they did not adequately report the performance of blind.

Excellent response (≥ 75% repigmentation)

All the studies reported the data of excellent response [14, 24–33]. The excellent response rates for patients in combination with phototherapy and tacrolimus group and phototherapy group were 62.97% and 45.89%, respectively. The pooled estimate suggested that patients in the combination group achieved a significantly higher excellent response rate than those in the phototherapy group (RR = 1.40, 95% CI 1.16, 1.69; $P < 0.001$) (Fig. 3). The test for heterogeneity was significant ($I^2 = 56.8\%$, $P = 0.001$). When we excluded the trial with outlier [28], the overall estimate changed a little (RR = 1.48, 95% CI 1.33, 1.65; $P < 0.001$), but the heterogeneity was still present ($I^2 = 55.4\%$, $P = 0.002$). Then, we further excluded the trial with small sample size [31], the pooled result did not alter substantially (RR = 1.43, 95% CI 1.28, 1.60; $P < 0.001$), but the degree of heterogeneity seemed to be higher than before ($I^2 = 66.9\%$, $P < 0.001$). We also excluded the remaining trials once at a time, but no meaningful information for the source of heterogeneity was found.

Subgroup analysis based on the site of lesion showed that, the superior effect of combination treatment over phototherapy alone was only observed on the face (RR = 1.60, 95% CI 1.21, 2.12; $P = 0.001$) and proximal limbs (RR = 2.76, 95% CI 1.38, 5.54; $P = 0.002$), but not on the trunk (RR = 0.59, 95% CI 0.31, 1.12; $P = 0.104$), and hand–foot (RR = 1.86, 95% CI 0.71, 4.90; $P = 0.208$) (Fig. 3).

Subgroup analysis based on the type of phototherapy suggested that both NB-UVB and EI, when added to tacrolimus, resulted in a significantly higher excellent response rate as compared with they were used alone (NB-UVB: RR = 1.28, 95% CI 1.09, 1.50, $P = 0.003$; EL: RR = 1.76, 95% CI 1.02, 3.03; $P = 0.044$).

Subgroup analysis based on the patients showed that the higher excellent response rate associated with combination treatment was observed in both adults (RR = 1.37, 95% CI: 1.13, 1.66; $P = 0.001$) and children patients (RR = 2.44, 95% CI 1.01, 5.90, $P = 0.048$).

Good response (50%–75% repigmentation)

Seven studies reported the data of good response [14, 24, 26, 27, 29–31]. The excellent response rate in combination and phototherapeutic groups was 19.87% and 27.06%, respectively. Pooled data demonstrated that there was no significant difference between the two groups in terms of good response rate (RR = 1.00, 95% CI 0.59, 1.69, $P = 1.000$) (Fig. 4). There was moderate heterogeneity across the included studies ($I^2 = 52.5\%$, $P = 0.017$).

Subgroup analysis based on the site of lesions showed that combination treatment of phototherapy and tacrolimus had comparable good response rate with phototherapy alone for lesions located in the face (RR = 0.84, 95% CI 0.46, 1.53, $P = 0.569$), trunk (RR = 3.51, 95% CI 0.79, 15.58, $P = 0.099$), and proximal limbs (RR = 1.35, 95% CI 0.31, 5.92, $P = 0.694$) (Fig. 4).

Subgroup analysis based on the type of phototherapy showed that both NB-UVB and EL, when added to tacrolimus, had similar good response rate with phototherapeutic monotherapy (NB-UVB: RR = 0.94, 95% CI 0.55, 1.62, $P = 0.819$; EL: RR = 2.17, 95% CI 0.47, 10.00; $P = 0.319$).

Subgroup analysis based on patients showed that adult and children patients who received combination treatment

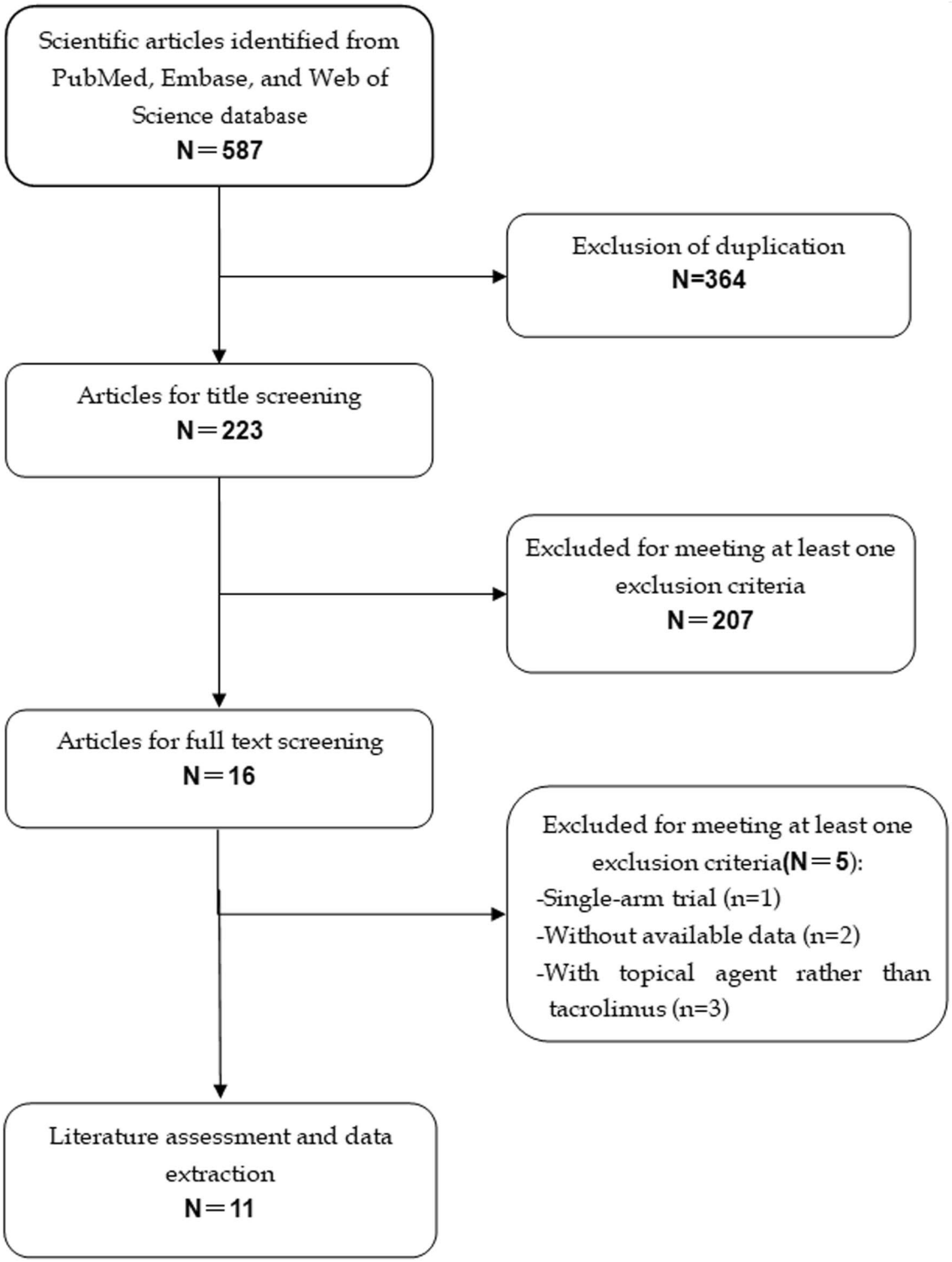

Fig. 1 Eligibility of studies for inclusion in the meta-analysis

Table 1 Baseline characteristics of patients in the trials included in the meta-analysis

Study	Country	Study design	Treatment regimen	No. of patients	Male/female	Vitiligo subtype	Age (mean ± SD, y)	Disease duration (year)
Lotti [14]	Italy	Comparative study	NB-UVB + 0.1% tacrolimus	59	NR	Segmental/nonsegmental	18-72	NA
			NB-UVB	100	NR		18–72	NA
Bilal [24]	Pakistan	RCT	NB-UVB + 0.1% tacrolimus	30	18/12	Segmental/nonsegmental	38.92 ± 6.35	NA
			NB-UVB + placebo	30	19/11		37.54 ± 7.04	NA
Ullah [25]	Pakistan	RCT	NB-UVB + 0.1%	47	16/31	NR	28.59 ± 8.86	NA
			NB-UVB	47	19/28		28.59 ± 8.86	NA
Dayal [26]	India	Open-label, comparative study	NB-UVB + 0.1% tacrolimus	20	9/11	Symmetrical	11.1 ± 2.9	3.2 ± 3.1
			NB-UVB	20	9/11		11.1 ± 2.9	3.2 ± 3.1
Passeron [27]	France	Randomized, intra-individual study	308-nm EL + 0.1% tacrolimus	14	NR	Symmetrical	36.6 (12–63)	18.1 (3–33)
			308-nm EL	14	NR		36.6 (12–63)	18.1 (3–33)
Bapur Erduran [28]	Turkey	Comparative study	308-nm EL + 0.1% tacrolimus	29	8/21	localized	30.6 ± 7.8	4
			308-nm EL	30	11/19		32.8 ± 8.6	3
Majid [29]	India	Randomized, intra-individual study	NB-UVB + 0.1% tacrolimus	74	33/41	Symmetrical	22.73 (12–42)	4.08
			NB-UVB	74	33/41		22.73 (12–42)	4.08
Klahan [30]	Thailand	Randomized, intra-individual study	NB-UVB + 0.1% tacrolimus	15	6/9	Generalized/focal	41.67 ± 11.65	< 5/6–10/> 10:7/3/5
			NB-UVB	15	6/9		41.67 ± 11.65	< 5/6–10/> 10:7/3/5
Satyanarayan [31]	India	Randomized, intra-individual study	NB-UVB + 0.1% tacrolimus	25	13/12	Generalized	14–36	NR
			NB-UVB	25	13/12		14–36	NR
Kawalek [32]	USA	RCT intra-individual study	E + 0.1% tacrolimus	8	3/5	Symmetrical	38 (31–51)	< 1/1–5/> 5:1/1/6
			EL	8	3/5		38 (31–51)	< 1/1–5/> 5:1/1/6
Nistico [33]	Italy	RCT	308-nm EL	20	10/10	Generalized/focal	26.4 ± 11.5	2.17
			308-nm EL + 0.1% tacrolimus	20	11/9		31.95 ± 14.07	2.5

SD standard deviation, NB-UVB Narrow-band ultraviolet B, EL excimer laser/light, NR not reported, NA not available

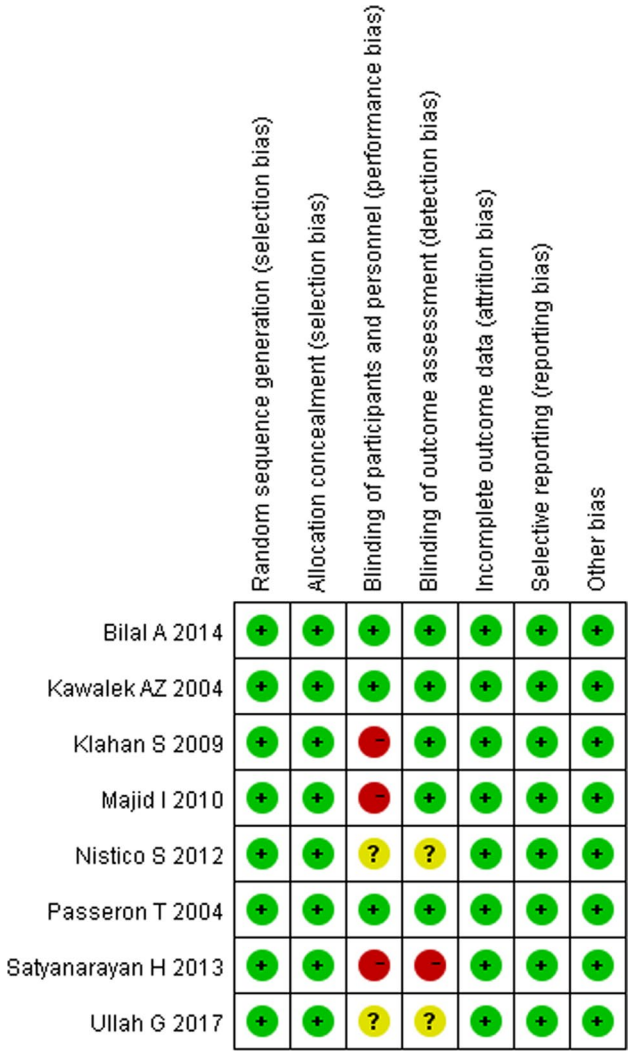

Fig. 2 Risk of bias summary

had similar good response rate with phototherapeutic monotherapy (adult: RR = 0.95, 95% CI 0.54, 1.67, $P = 0.863$; children: RR = 1.69, 95% CI 0.38, 7.59, $P = 0.493$).

Moderate response (25%–50% repigmentation)

Six studies reported the data of moderate response [14, 24, 26, 27, 29, 31]. The moderate response rate in combination and phototherapy groups was 11.62% and 11.80%, respectively. The pooled result showed that there was no significant difference between the two groups in terms of moderate response rate (RR = 0.91, 95% CI 0.60, 1.38; $P = 0.653$). The test for heterogeneity was not significant ($I^2 = 0.0\%$, $P = 0.755$).

Subgroup analysis based on the site of lesions showed that, combination treatment of phototherapy and tacrolimus had comparable moderate response rate with phototherapy alone for lesions located in face (RR = 0.65, 95% CI 0.24, 1.72, $P = 0.382$), trunk (RR = 0.33, 95% CI 0.02, 5.97, $P = 0.455$), proximal limbs (RR = 15.00, 95% CI 0.95, 236.42, $P = 0.054$), and hand–foot (RR = 1.00, 95% CI 0.10, 9.61; $P = 1.00$).

Subgroup analysis based on the type of phototherapy suggested that, both NB-UVB and EL, when in combination with tacrolimus, had similar moderate response rate with phototherapeutic monotherapy (NB-UVB: RR = 0.94, 95% CI 0.61, 1.45, $P = 0.772$; EL: RR = 0.58, 95% CI 0.11, 3.13; $P = 0.526$).

Subgroup analysis based on patients demonstrated that both adult and children patients who received combination treatment achieved a similar moderate response rate with those with phototherapy alone (adult: RR = 0.76, 95% CI 0.48, 1.20, $P = 0.234$; children: RR = 2.43, 95% CI 0.75, 7.91, $P = 0.141$).

Poor response (< 25% repigmentation)

Seven studies reported the data of poor response rate [14, 24, 26, 27, 29, 31, 33]. Overall, the poor response rate for combination treatment was 5.39%, as compared with 14.33% for phototherapeutic monotherapy, respectively. The summarized data showed that the poor response rate was significantly lower in the combination treatment group than in the phototherapy group (RR = 0.37, 95% CI 0.22, 0.61; $P = 0.001$) (Fig. 5). The test for heterogeneity was not significant ($I^2 = 38.6\%$, P = 0.101).

Subgroup analysis based on the site of lesions showed that, the combination treatment had comparable poor response rate with phototherapy alone for lesions located in face (RR = 0.17, 95% CI 0.02, 1.30, P = 0.088), trunk (RR = 0.20, 95% CI 0.01, 2.98, P = 0.243), and hand–foot (RR = 1.00, 95% CI 0.32, 3.10; P = 1.00). However, for the lesions located in proximal limbs, the poor response rate was lower in the combination treatment group than in the phototherapy group (RR = 0.09, 95% CI 0.01, 0.60, P = 0.013) (Fig. 5).

Subgroup analysis based on the type of phototherapy suggested that, both NB-UVB and EL, when in combination with tacrolimus, had lower poor response rate with phototherapeutic monotherapy (NB-UVB: RR = 0.47, 95% CI 0.27, 0.81, P = 0.007; EL: RR = 0.10, 95% CI 0.02, 0.52; P = 0.006).

Subgroup analysis based on patients demonstrated that both adult and children patients who received combination treatment achieved lower poor response rate than those with phototherapy alone (adult: RR = 0.47, 95% CI 0.27, 0.81, P = 0.007; children: RR = 0.13, 95% CI 0.03, 0.52, P = 0.004).

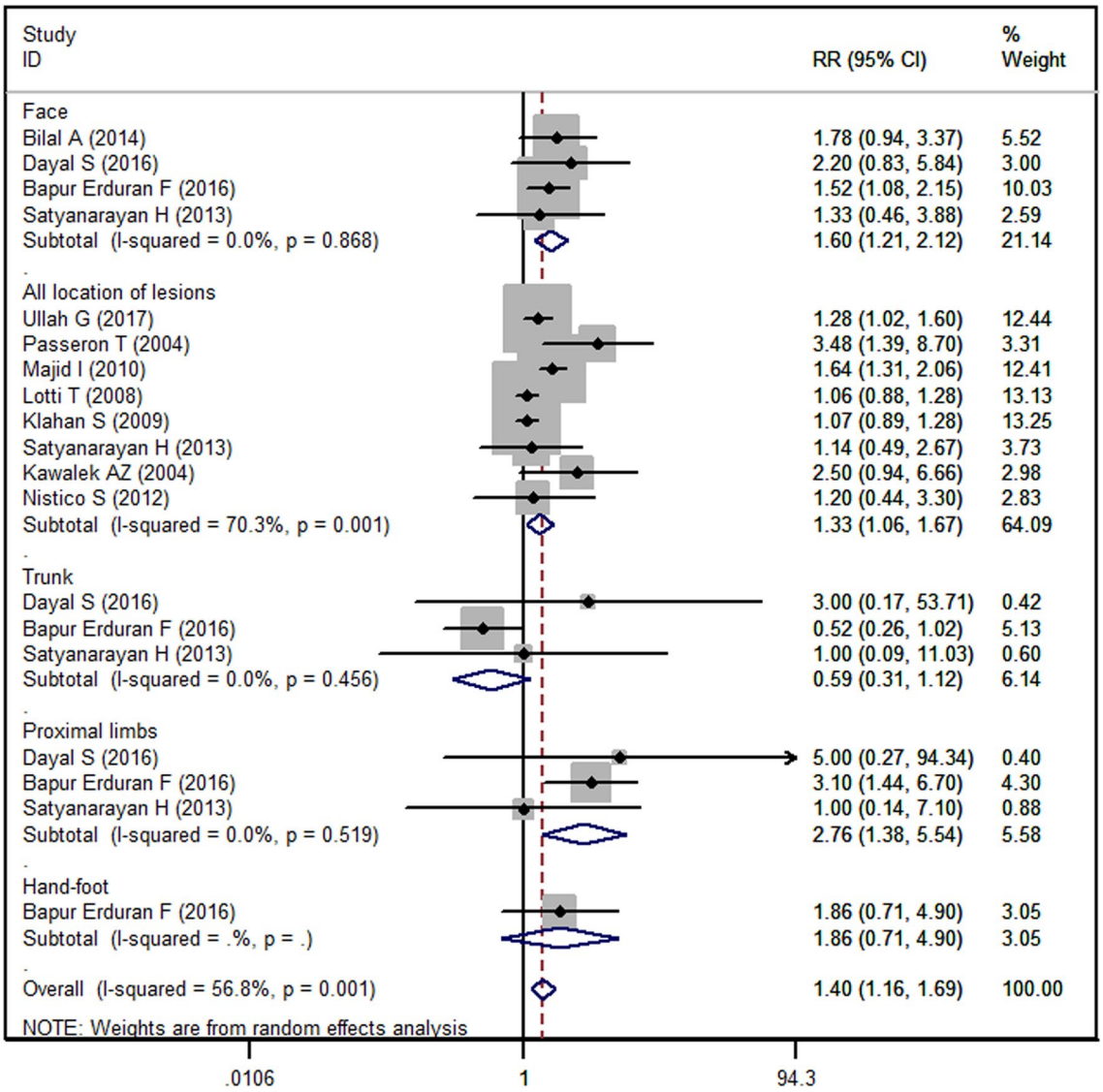

Fig. 3 Forest plot showing the effect of phototherapy and tacrolimus on the excellent response of repigmentation

Meta-regression

Table 2 shows the results of a multivariate meta-regression for demographic (mean age and gender) and clinical variables (disease duration, family history, and type of vitiligo). The analysis results suggested that age was a predictive factor for the treatment effect, in which children had a high excellent response rate.

Publication bias

The results of publication bias suggested that there was no evidence of publication bias across the included studies (Egg test, P = 0.349; Begg test, P = 0.516).

Discussion

Our results suggested that combination treatment significantly improved the excellent response rate (≥ 75% repigmentation) and reduced the poor response rate (< 25% repigmentation). Subgroup analysis showed that the combination treatment was effective in the treatment of vitiligo for inducing repigmentation, especially when located in the face and proximal limbs. Both NB-UVB and EL showed a beneficial effect in vitiligo when they were added into the treatment of tacrolimus. We also identified that age was a predictive factor that influenced the effects of combination treatment, in which children had an excellent high response to the combination treatment.

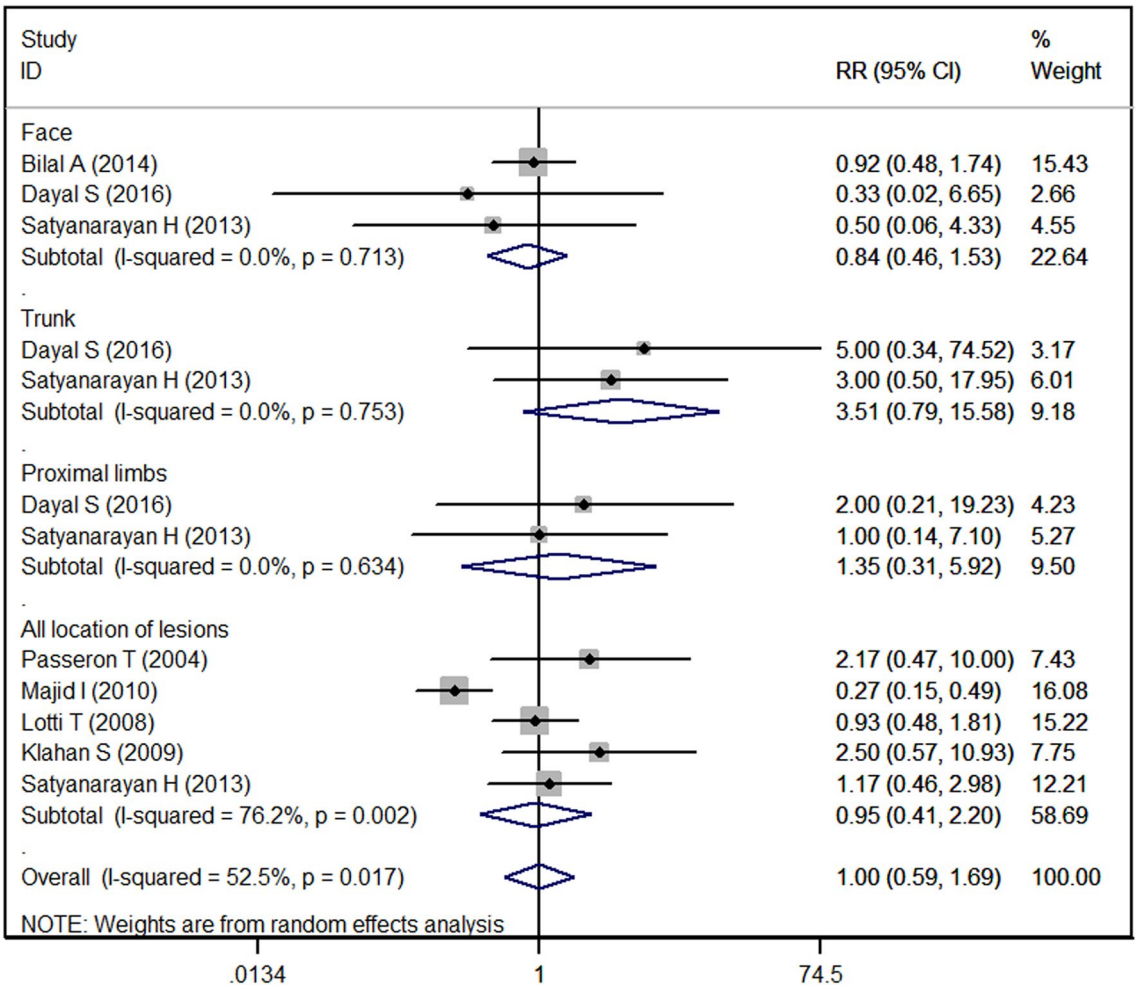

Fig. 4 Forest plot showing the effect of phototherapy and tacrolimus on the good response of repigmentation

Although several previous trials [34–36] have demonstrated that NB-UVB phototherapy was effective in the improvement of repigmentation for vitiligo, the maximally aggressive phototherapy may fail repigment vitiliginous lesions. Thus, other modalities, such as topical tacrolimus, are needed in combination with NB-UVB to treat vitiligo. There are two requirements for the optimal repigmentation of vitiligo macules: first, the disease process is prevented by an immunomodulator, which tacrolimus can provide; second, the melanoblasts are proliferated and migrated by a stimulator, which the phototherapy can induce [26]. Through activating the pathways of melanocyte mitogenesis, melanocyte migration, and melanogenesis, tacrolimus plays a synergistic action with phototherapy [1]. Because of the synergistic action, the combination treatment may result in higher efficacy.

NB-UVB has been used along with topical tacrolimus to increase its efficacy and shorten the total duration of treatment. The advantages of NB-UVB in the treatment of vitiligo included its extremely low side-effect, particularly on the systemic front, and its established use in children and adults, even in pregnant females [37]. The advantage of tacrolimus included that it does not cause skin atrophy even in long-term therapy [38, 39]. Moreover, the use of tacrolimus may also be helpful in the prevention of NB-UVB-associated erythema by inhibiting early-phase events of the inflammatory process [40, 41]. Majid et al. [29] performed a left–right comparison study to assess whether topical tacrolimus would enhance the efficacy of NB-UVB therapy in vitiligo. They found that the addition of tacrolimus significantly improved the extent of overall repigmentation, as well as reduced the cumulative NB-UVB dose that needed to achieve a therapeutic benefit in vitiligo [29].

Bilal et al. [24] conducted a randomized, double-blind, placebo-controlled trial to compare the effects of combined treatment of NB-UVB and topical tacrolimus with NB-UVB alone in 60 patients with vitiligo affecting face and neck. Their results suggested that the excellent response rate was

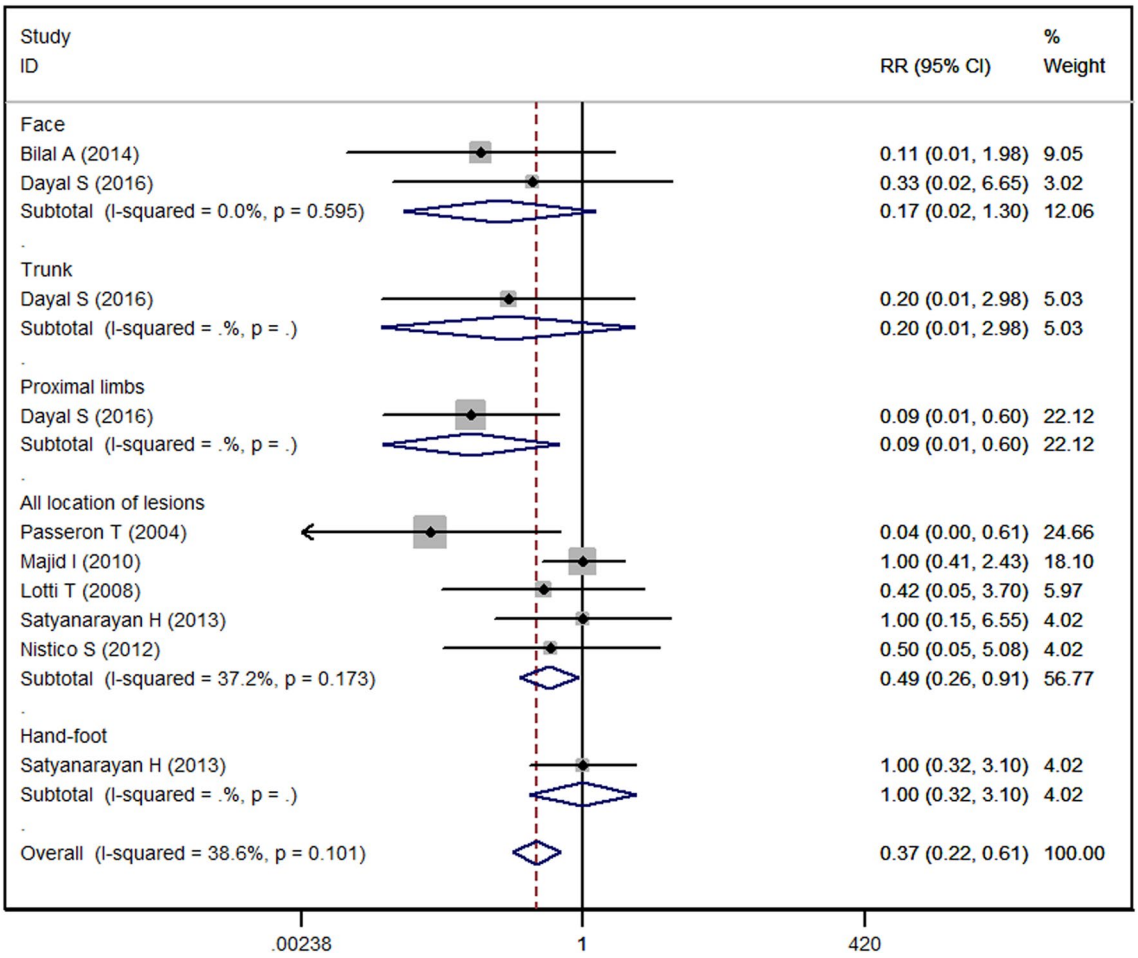

Fig. 5 Forest plot showing the effect of phototherapy and tacrolimus on the poor response of repigmentation

Table 2 Results of multivariate meta-regression analyses for demographic (mean age and gender) and clinical variables (disease duration, family history, and type of vitiligo) to predict effects of tacrolimus plus phototherapy on the excellent response rate

Covariate	Coefficient	95% CI	t value	P value
Age	− 1.4743	− 2.1211, − 0.8276	− 4.81	< 0.001
Gender	− 0.0846	− 0.6346, 0.4653	− 0.32	0.749
Disease duration	0.0254	− 0.7457, 0.7966	0.07	0.945
Family history	− 0.3282	− 1.0341, 0.7757	− 0.98	0.340
Type of vitiligo	− 0.3059	− 0.1.002, 0.3899	− 0.93	0.367

higher in the combination group (53.3%) than in the monotherapy group (30%) [24]. Moreover, none of the patients showed a poor response in the combination group as compared with 4 (13.3%) patients in the monotherapy group. The authors concluded that the combined treatment of tacrolimus and NB-UVB was more effective than NB-UVB alone in the treatment of vitiligo affecting face and neck. Contradictory results were observed in another randomized, placebo-controlled, double-blind trial, in which the addition of tacrolimus NB-UVB did not show superior effect than NB-UVB alone in the treatment of vitiligo [42]. In that study, eight patients were treated for 12 weeks, with NB-UVB 3 times per week. The average improvement of target lesions at 12 weeks was 49.24% and 41.28% in the tacrolimus- and placebo-treated group, respectively [42]. There was no significant difference between the two groups.

The authors concluded that the combination of topical tacrolimus and NB-UVB was not more efficacious than NB-UVB alone in the treatment of vitiligo. The reasons for the negative results were not discussed in that study. We think this can be attributed to the small sample size and short treatment duration.

Several factors seemed to have an impact on the degree of treatment response, including disease location, skin color, and age. Patients who had darker skin tones, especially those whose disease located in the head and neck, would achieve the best response. Lee et al. [43] reported that a mild response was found in 73.1% of patients in the face and

neck, whereas such a response was not found for other body parts. Age was another factor affecting the treatment effect. There were studies reporting children had a better response than adults [44, 45], which were consistent with the finding in this study. Some hypotheses may explain these results. Served as the reservoirs of melanocytes, hair follicles are built in the early fetal period and move apart according to the growth of the skin after birth [46]. Since children have higher hair follicle density than adults, they respond better than adults [47].

Conclusions

The present meta-analysis showed that the combination of topical tacrolimus and phototherapy was effective in the treatment of vitiligo than phototherapy alone. It can improve the extent of skin repigmentation and decrease the psychological distress of patients due to cosmetic disfigurement caused by vitiligo. However, considering the potential limitations, more large-scale, well-designed RCTs are needed to verify our findings.

Author contributions YD and XS contributed to the study design; all authors collected the data and performed the data analysis; all authors prepared the manuscript.

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Availability of data and material The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest All the authors declare that they have no conflict of interest.

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