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Review Article

The Efficacy, Safety, and Recurrence Rate of Diphenylcyclopropenone Topical Immunotherapy for Alopecia Areata: A Systemic Review and Meta-Analysis

Jiaping Zhu, Rui Qiao, Yufen Li, Xuemei Lan, Xiangdong Gong, and Yiqun Jiang

Hospital for Skin Diseases, Institute of Dermatology, Chinese Academy of Medical Sciences & Peking Union Medical College, 12 Jiangwangmiao Street, Nanjing, Jiangsu 210042, China

Correspondence should be addressed to Yiqun Jiang; yiqunjiang@qq.com

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Background and Objective. Diphenylcyclopropenone topical immunotherapy is widely used in the treatment of alopecia areata. However, previous studies have shown significant differences in its efficacy. We conducted this systemic review and meta-analysis to investigate the efficacy, safety, and recurrence rate of diphenylcyclopropenone topical immunotherapy for alopecia areata. *Methods*. Literatures related to diphenylcyclopropenone topical immunotherapy for alopecia areata between January 1st, 2002, and July 2nd, 2022, were searched in the following databases: PubMed, Embase, Cochrane Library, Sinomed, WanFang Data, and Chinese Medical Journal Network. *Results*. This meta-analysis included a total of 40 moderate to high quality studies involving 3,002 patients. The overall rate of any hair regrowth was 69%, and the overall rate of complete hair regrowth was 23%. The rate of any hair regrowth in patients with alopecia totalis or alopecia universalis was 42%, and the rate of any hair regrowth in patients with other types of alopecia areata was 75%. Common side effects were mild contact dermatitis (36%), severe contact dermatitis (31%), regional lymphadenopathy (22%), hyperpigmentation (22%), and hypopigmentation (7%). The recurrence rate was 37%. *Conclusion*. Diphenylcyclopropenone topical immunotherapy is an effective treatment for various types of alopecia areata, and most of its common side effects are acceptable.

1. Introduction

Alopecia areata (AA) is a common cause of hair loss, characterized by the sudden appearance of well-defined patches of hair loss [1]. With a prevalence of approximately 2% in the general population, AA has a significant impact on the quality of life and increases the risk of psychopathology [2]. 74% of the AA patients suffer from mental disorders at least once during their lifetime [3]. Despite extensive research, the pathogenesis of AA remains poorly understood. However, current understanding suggests that it is an autoimmune disease resulting from the breakdown of immune privilege of the hair follicle [4]. This complex process involves abnormal presentation of hair follicle antigens, activation of CD8 + NKG2D + T cells, overexpression of inflammatory cytokines (such as IFN-γ and IL-15), and other contributing factors [1, 2, 4]. Given the close link between AA pathogenesis and autoimmune inflammation, therapeutic interventions for AA have focused primarily on modulating the immune microenvironment. These treatment options include topical or intralesional administration of corticosteroids as well as the systemic application of corticosteroids or other immunosuppressive agents [5]. Recent studies have shown remarkable efficacy of JAK inhibitors, including baricitinib and tofacitinib, in the treatment of moderate to severe AA [6, 7]. These results underscore the importance of JAK inhibitors in the treatment of AA by targeting the immune and inflammatory pathways. However, there are still many cases of severe or treatment-resistant alopecia areata, and effective long-term management of these cases remains a significant challenge.

Table 1: Search strategy (English version).

Databases	Search strategy
PubMed	("Alopecia areata" or "alopecia circumscripta" or "totalis" or "universalis") and ("topical immunotherapy" or "diphenylcyclopropenone" or "diphencyprone" or "DPCP" or "DPCP")
Embase	("Alopecia areata" or "alopecia circumscripta" or "totalis" or "universalis" or "alopecia universalis" or "alopecia totalis") and ("topical immunotherapy" or "diphenylcyclopropenone" or "diphencyprone" or "dpcp" or "dcp")
Cochrane Library	("Alopecia areata" or "alopecia areata fere totalis" or "alopecia areata totalis") and ("topical immunotherapy" or "diphenylcyclopropenone" or "diphencyprone")
WanFang Data	(Topical immunotherapy) or (diphenylcyclopropenone) or (DPCP) and (alopecia areata) or (alopecia totalis) or (alopecia universalis)
Sinomed	(Alopecia areata) or (alopecia totalis) or (alopecia universalis) and (topical immunotherapy) or (diphenylcyclopropenone) or (DPCP)
Chinese Medical Journal Network	(Alopecia areata or alopecia totalis or alopecia universalis) and (topical immunotherapy or diphenylcyclopropenone or DPCP)

Topical immunotherapy is a commonly used therapy for severe or recurrent AA. The application of topical sensitizers such as diphenylcyclopropenone (DPCP) to the lesions of AA patients can repeatedly induce contact dermatitis and then, a certain remission rate can be achieved after a period of maintenance therapy [8]. Although there are potential side effects such as severe eczema and lymphadenopathy [5], they are generally more tolerable than the side effects associated with systemic immunosuppressants. The mechanism underlying the efficacy of topical immunotherapy remains unclear, but potential explanations include antigen competition, modulation of perifollicular lymphocyte subsets, and reduction of proinflammatory Th1 and Th17 cytokine levels [8]. In addition to DPCP, other sensitizers used in topical immunotherapy include squaric acid dibutyl ester (SADBE) and dinitrochlorobenzene (DNCB) [8]. The latter is no longer used due to its teratogenicity and carcinogenicity. DPCP is the most commonly used sensitizer because it is more stable in acetone solution and is less expensive than SADBE.

There has been a surge of new, high-quality clinical studies investigating DPCP topical immunotherapy for AA. However, these studies have yielded heterogeneous results, reporting varying hair regrowth rates, ranging from as low as 34.4% (21/61) [9] to as high as 92.3% (36/39) [10]. To provide a comprehensive and up-to-date assessment of DPCP as a therapeutic option for AA, we conducted a meta-analysis based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) process. Our study reviewed relevant studies conducted over the past 20 years and quantitatively evaluated the efficacy, safety, and relapse rate of DPCP in the treatment of AA.

2. Materials and Methods

2.1. Search Strategy. A comprehensive search for English and Chinese literature related to DPCP in the treatment of AA was conducted in the following databases: PubMed, Embase, Cochrane Library, Sinomed, WanFang Data, and Chinese Medical Journal Network. The articles included in the search were published between January 1st, 2002, and July 2nd, 2022. The search strategies used in each database are shown in Tables 1 and 2.

2.2. Study Selection. The literature obtained was summarized in Endnote X9.3.2. Study selection and quality assessment were performed independently by two authors (Z.J.P and J.Y.Q) according to the title and abstract. When the information provided by the title and abstract was insufficient, the full text was referred to. When the two authors had different opinions, consensus was reached after consultation with the third author (G.X.D).

2.2.1. Diagnostic Criteria for AA. The diagnosis of AA and the differentiation of AA types were based on clinical manifestations and medical history.

2.2.2. Inclusion Criteria. The inclusion criteria were as follows: (1) The research type: clinical trial/retrospective analysis; (2) the study population: patients with AA; (3) the intervention: DPCP topical immunotherapy; and (4) the outcome indicators included at least efficacy.

2.2.3. Exclusion Criteria. The exclusion criteria were as follows: (1) The type of research: studies with only in vitro or in vivo research or reviews; (2) the subject of research: irrelevant to DPCP topical immunotherapy for AA; (3) the intervention: sensitizers other than DPCP were used, or other drugs were used concomitantly, or the DPCP monotherapy group was not set as a separate group, or data on the DPCP monotherapy group were not provided; (4) the research method: questionnaires were used as the main measure; (5) the response of the eyebrow area to DPCP in patients with AA was the only outcome observed; (6) the number of patients in the DPCP treatment group was less than 20 (this is not required for subgroup analysis); (7) the focus was on sensitization effects rather than efficacy; (8) detailed outcomes such as efficacy were not reported; (9) the literature was written in language other than Chinese and English; and (10) clinical studies not completed.

Table 2: Search strategy (Chinese pinyin version).

Databases	Search strategy
PubMed	("Alopecia areata" or "alopecia circumscripta" or "totalis" or "universalis") and ("topical immunotherapy" or "diphenylcyclopropenone" or "diphencyprone" or "DPCP" or "DPCP")
Embase	("Alopecia areata" or "alopecia circumscripta" or "totalis" or "universalis" or "alopecia universalis" or "alopecia totalis") and ("topical immunotherapy" OR "diphenylcyclopropenone" or "diphencyprone" or "dpcp" or "dcp")
Cochrane Library	("Alopecia areata" or "alopecia areata fere totalis" or "alopecia areata totalis") and ("topical immunotherapy" or "diphenylcyclopropenone" or "diphencyprone")
WanFang Data	(Ju bu mian yi zhi liao) or (er ben ji huan bing xi tong) or (DPCP) and (ban tu) or (pu tu) or (quan tu)
Sinomed	(Ban tu) or (pu tu) or (quan tu) and (ju bu mian yi zhi liao) or (er ben ji huan bing xi tong) or (DPCP)
Chinese Medical Journal Network	(Ban tu or pu tu or quan tu) and (ju bu mian yi zhi liao or er ben ji huan bing xi tong or DPCP)

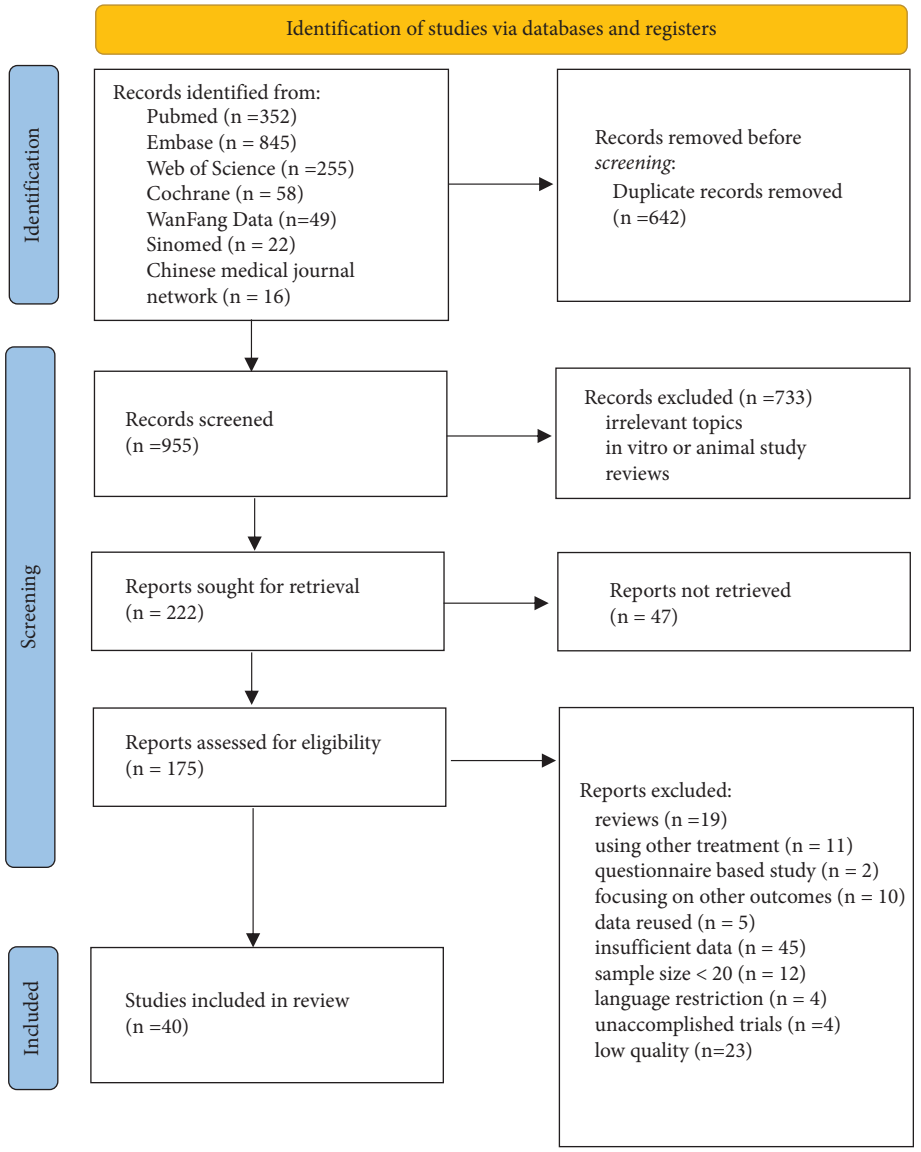

Figure 1: PRISMA flow diagram of study selection.

The PRISMA flow diagram is shown in Figure 1.

2.3. Quality Assessment. The methodological index for nonrandomized studies (MINORS) was used to assess the quality of the included studies. For studies that did not apply to MINORS entries, their quality was assessed based on the following factors: the type of research design (randomized controlled trials, prospective clinical trials, and retrospective analysis), whether the study reported the proportion of areata totalis (AT) and areata universalis (AU) patients, whether the study reported the criteria for assessing hair growth outcomes, whether the study reported adverse effects, and whether the study reported the definition of recurrence.

2.4. Data Extraction. The following items of data were extracted from each study: study year, author, title, type of study design (e.g., prospective or retrospective), study setting, region, mean age, sex ratio, disease duration of the study population, protocol of DPCP application, evaluation criteria for hair regrowth, rate of any hair regrowth (any improvement from a baseline), rate of complete hair regrowth (100% terminal hair growth was achieved), prevalence of adverse effect, and recurrence rate. The data collection process was completed using WPS Office 4.6.2. The data were collected independently by two researchers (Z.J.P and J.Y.Q) and compared for consistency.

2.5. Data Synthesis. The Shapiro–Wilk normality test was performed on the data before synthesis to confirm that they conformed to a normal distribution. Because most of the included studies were retrospective analyses or single-arm clinical trials (without a control group), only the regrowth rate was used as an outcome measure. Because the definitions and stratification criteria for hair regrowth outcomes varied widely among the studies, we classified hair regrowth outcomes as either any regrowth or complete regrowth. The rate of each outcome was then synthesized. If the information provided in the article was insufficient to determine what level of regrowth a group belonged to, the group was categorized as lower. In addition, the recurrence rate and the incidence of side effects were synthesized. Only the side effects reported by 10 or more studies were included. To help identify factors that may have an impact on the response to the treatment, subgroup analysis was performed according to the type of AA in studies that reported the proportion of AT and AU patients and their hair regrowth outcome. We also performed subgroup analyses according to age, disease duration, nail involvement, history of atopic disease, family history, and SALT (Severity of Alopecia Tool [11]) score in the relevant studies where data were available. Further subgroup analysis was performed by study language and region. After synthesis, all data were displayed using forest plots. Because the I^2 test indicated high heterogeneity among study results, random effects models were used for the meta-analysis. Sensitivity analysis was used to assess sources of heterogeneity after pooling effects. Egger's regression test was used to assess publication bias. All data analyses were performed using *R* 4.2.1 and the *R* package "meta."

3. Results

3.1. Study Characteristics and the Quality Assessment. A total of 40 moderate to high quality studies were included, involving 3,002 patients. Among them, 19 were retrospective analyses, 16 were single-arm clinical trials, 2 were controlled clinical trials, and 3 were randomized controlled trials. Regarding populations, 2 studies were conducted in African, 20 in Asian, 14 in European, and 4 in North American populations. The proportion of patients with AT or AU was reported in 31 studies. All studies reported the rate of any hair regrowth. There were 16 studies reporting the complete regrowth rate and 15 studies reporting the recurrence rate, 7 of which reported the definition of recurrence. However, no studies reported the duration of follow-up. There were 18 studies that reported the rate of any hair regrowth in the AT/AU group, including 471 patients with AT/AU and 526 patients with other AA types. Seven studies reported any hair regrowth rates in different age groups, 5 studies reported any hair regrowth rates in different disease duration groups, 4 studies reported any hair regrowth rates in groups with and without nail involvement, 7 studies reported any hair regrowth rates in groups with and without family history, 8 studies reported any hair regrowth rates in groups with and without history of atopic disease, and 6 studies reported any hair regrowth rates in different SALT score groups. Regarding the incidence of side effects, mild contact dermatitis (mild to moderate pruritus and erythema) was reported in 15 studies, severe contact dermatitis (vesicles, erosions, and systemic symptoms) in 16 studies, hyperpigmentation in 12 studies, hypopigmentation in 10 studies, and regional lymphadenopathy in 17 studies. Twenty-seven studies evaluated hair growth outcomes using SALT or other quantitative criteria. Qualitative criteria (e.g., stratification of results into no response, scattered pigmented terminal hair, terminal hair growth but still patchy alopecia, and complete terminal hair growth) were used in 13 studies.

3.2. Hair Regrowth Rate. For AA after DPCP treatment, the overall rate of any hair regrowth was 69%, 95% CI (0.64, 0.73) (Figure 2), and the overall complete regrowth rate was 23%, 95% CI (0.16, 0.30) (Figure 3). Sensitivity analyses were performed, and all estimates differed by <3% from the original analyses. Egger's regression test indicated that publication bias was not significant ($p = 0.7341$).

As for the results of the subgroup analysis, only patients in the AT/AU group had a worse response to DPCP treatment. Also, when grouped by other factors such as age and disease duration, there was no significant difference in patient outcomes. The rate of any hair regrowth in the AT/AU group was 42%, 95% CI (0.33, 0.51), while the rate of any hair regrowth in patients with other AA types was 75%, 95% CI (0.67, 0.83), and there was a significant difference between the two groups ($p < 0.01$) (Figure 4). The rate of any

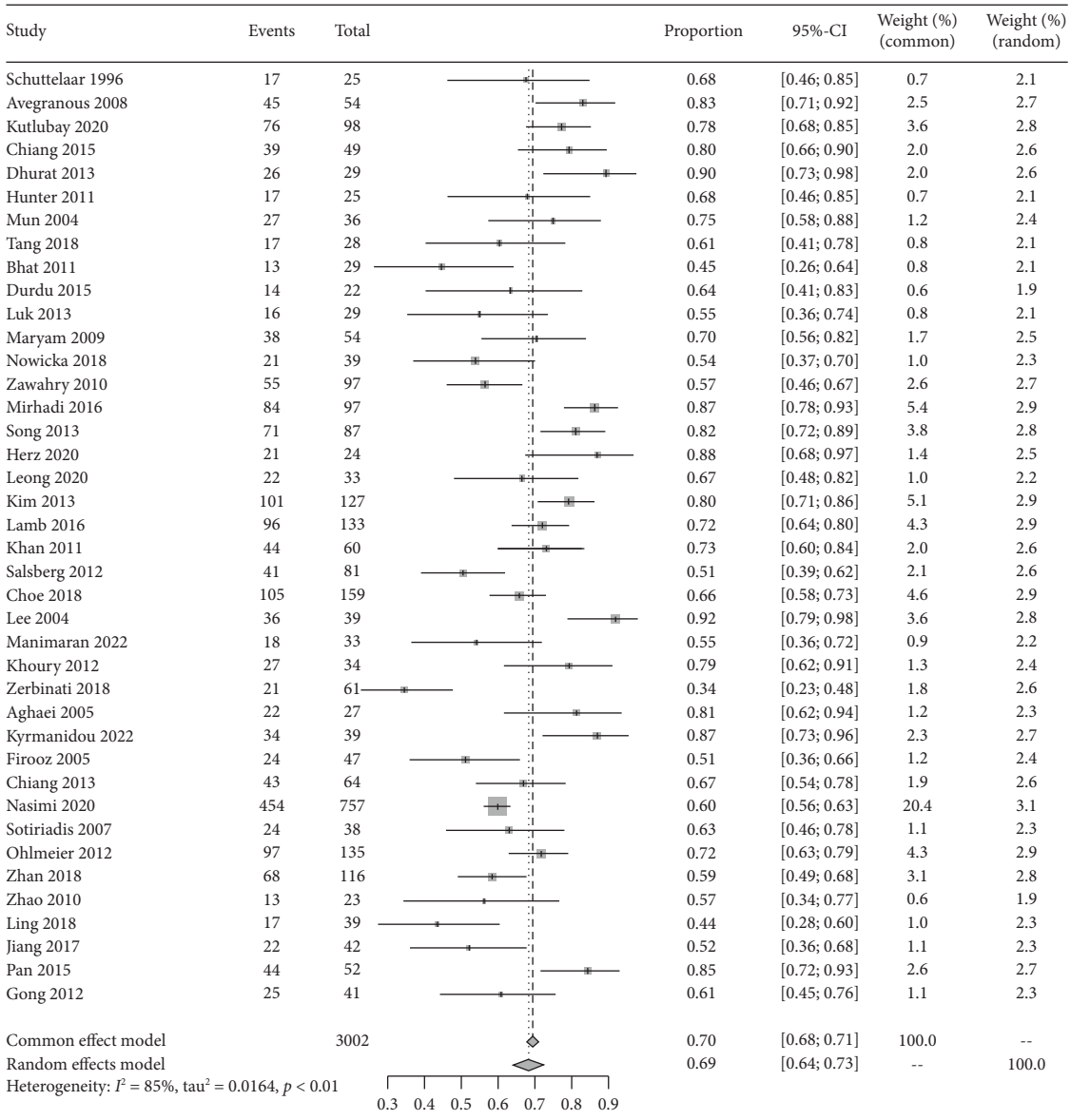

Figure 2: Overall any regrowth rate.

hair regrowth was 48%, 95% CI (0.35, 0.62) in patients aged <18 years and 59%, 95% CI (0.51, 0.67) in patients aged ≥18 years, with no significant difference observed between the two groups (p = 0.19) (Supplementary Figure 1). Similarly, in patients with disease duration ≥10 years, the rate of any hair regrowth was 48%, 95% CI (0.29, 0.67), while in patients with disease duration <10 years, the rate of any hair regrowth was 69%, 95% CI (0.60, 0.79), with no significant difference between the two groups (p = 0.06) (Supplementary Figure 2). Regarding nail involvement, the rate of any hair regrowth in patients with nail involvement was 40%, 95% CI (0.18, 0.63), and the rate of any hair regrowth in patients without nail involvement was 67%, 95% CI (0.51, 0.82), with no significant difference between the two groups (p = 0.06) (Supplementary Figure 3). Furthermore, there was no significant difference in the rate of any hair regrowth between patients with a history of atopic disease (55%, 95% CI (0.44, 0.66)) and those without (59%, 95% CI (0.49, 0.70)) (p = 0.58) (Supplementary Figure 4). Similarly, in patients with a family history of AA, the rate of any hair regrowth was 52%, 95% CI (0.29, 0.75), and in those without a family history of AA, the rate of any hair regrowth was 55%, 95% CI (0.47, 0.63), with no significant difference between the two groups (p = 0.80) (Supplementary Figure 5). The any hair regrowth rate was 64%, 95% CI (0.40, 0.89) in patients with SALT <50 and 49%, 95% CI [0.40, 0.57] in patients with SALT ≥50, with no significant difference between the two groups (p = 0.24) (Supplementary Figure 6). In addition, subgroup analysis was performed for all studies grouped by region and language, and there was no significant difference between regions and languages (Supplementary Figures 7–10).

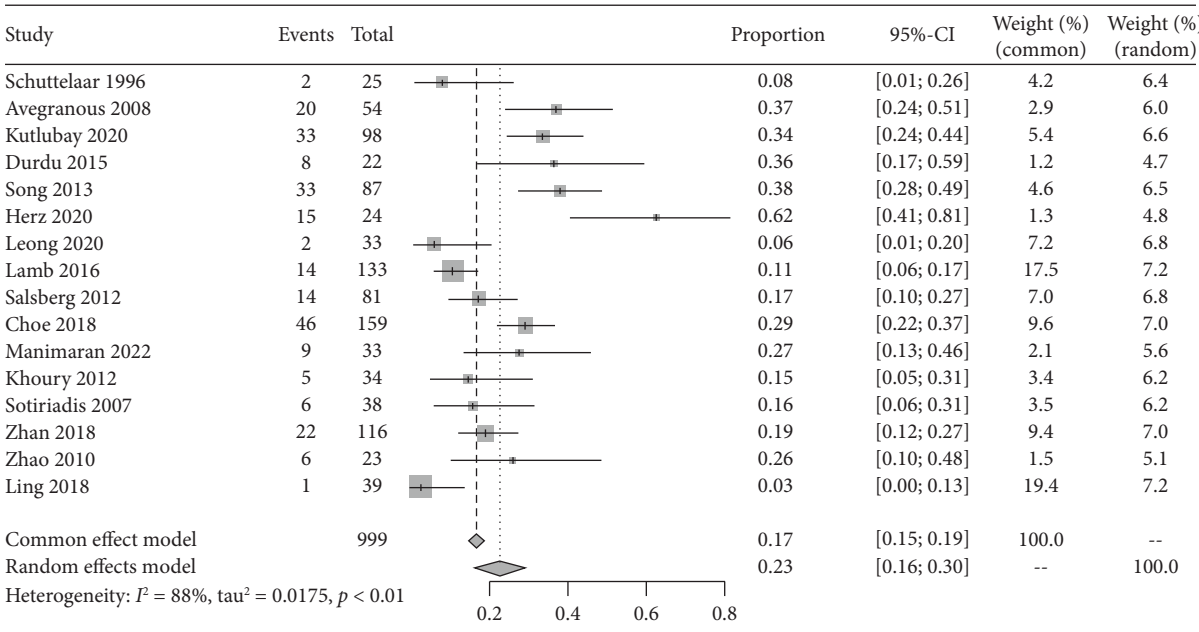

Figure 3: Complete regrowth rate.

3.3. Adverse Effects. The incidence of mild contact dermatitis was 36%, 95% CI (0.23, 0.56); severe contact dermatitis was 31%, 95% CI (0.18, 0.43); regional lymphadenopathy was 22%, 95% CI (0.12, 0.33); hyperpigmentation was 22%, 95% CI (0.13, 0.31); and hypopigmentation was 7%, 95% CI (0.03, 0.13) (Figures 5–9). Egger's regression test suggested that there was significant publication bias in the estimates of the incidence of the abovementioned adverse effects (mild contact dermatitis $p < 0.0001$, severe contact dermatitis $p < 0.0001$, regional lymphadenopathy $p = 0.0348$, hyperpigmentation $p = 0.0001$, and hypopigmentation $p = 0.0006$). Among them, mild contact dermatitis and hypopigmentation tended to be reported at a lower incidence, while severe contact dermatitis, regional lymphadenopathy, and hyperpigmentation tended to be reported at a higher incidence.

3.4. Recurrence Rate. The recurrence rate for AA treated with DPCP topical immunotherapy was 37%, 95% CI [0.23, 0.50] (Figure 10). Egger's test indicated a significant publication bias ($p = 0.0008$), and funnel plots showed that the studies tended to report higher recurrence rates.

4. Discussion

4.1. Efficacy. This meta-analysis included the largest number of patients to our knowledge. The results showed that for all the AA patients, the rate of any hair regrowth was about 69%, while the complete regrowth rate was about 23%. The rate of any hair regrowth was about 42% in AT/AU and 75% in other AA types. In comparison, the $SALT_{50}$ (defined as a decrease in the SALT score of at least 50% from the baseline) remission rate at week 16 was 29.9% in AA patients with SALT ≧50 who received baricitinib at a dose of 4 mg/day [12]. Considering that the typical course of DPCP topical immunotherapy spans 16 weeks, our assessment indicates a sufficiently high response rate. However, the existing evidence is limited in directly comparing the efficacy of DPCP with other treatments. Therefore, further research and larger-scale studies are needed to optimize the treatment regimens for AA.

Our results are in general agreement with the findings of Lee et al. in 2017, which reported a 63.8% any hair regrowth rate and 30.7% complete regrowth rate in all alopecia areata (AA) patients, as well as 75.5% and 51.6% any hair regrowth rate in patchy AA and alopecia totalis/alopecia universalis (AT/AU) patients, respectively [13]. The meta-analysis conducted by Lee et al. included literature in English and Korean, whereas our study encompassed literature in English and Chinese. This further validates the results of our subgroup analysis that the DPCP treatment of AA has similar efficacy across studies in different regions and languages.

Moreover, subgroup analyses did not confirm statistical differences in treatment response between patients of different age, disease duration, or SALT scores or between patients with or without family history, history of atopic disease, or nail involvement. However, the current conclusions still lack robustness as only a limited number of studies have reported patient outcomes based on specific subgroups of the abovementioned factors.

Despite the limitations, our study provides evidence that DPCP is a feasible treatment option with demonstrated efficacy for a diverse population of patients with alopecia areata. This finding is particularly significant for certain specific patient groups, such as pediatric patients. Treatment options for children with AA are extremely limited. Some studies recommend only topical glucocorticoids [5]. Indeed, topical steroids may not always be effective and it is in such

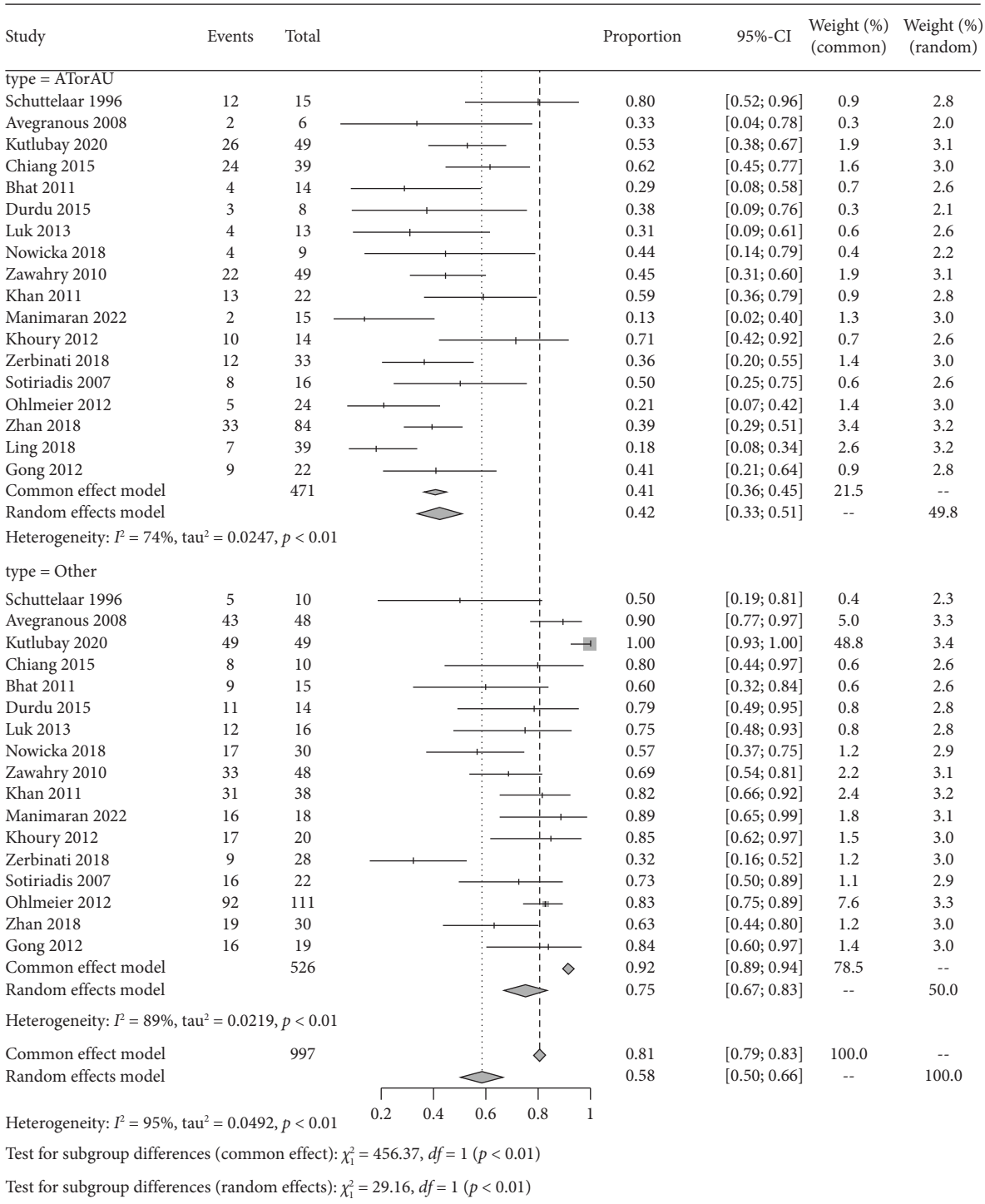

Figure 4: Any regrowth rate (subgroup analysis according to the type of alopecia areata).

cases that DPCP may be particularly valuable, especially given its lower cost and better tolerability compared to immunosuppressants.

4.2. Adverse Effects. The standard protocol of DPCP topical immunotherapy for AA requires induction of allergic contact dermatitis, so mild pruritus and eczema are common adverse reactions. According to the literature included in this study, adverse reactions such as severe contact dermatitis, regional lymphadenopathy, hyperpigmentation, and hypopigmentation have also been reported. Egger's regression test for publication bias analysis showed that investigators tended to report a lower incidence of mild contact dermatitis. This may be due to different definitions of adverse effects used by the investigators. Mild contact dermatitis is an expected normal reaction. Therefore, it may

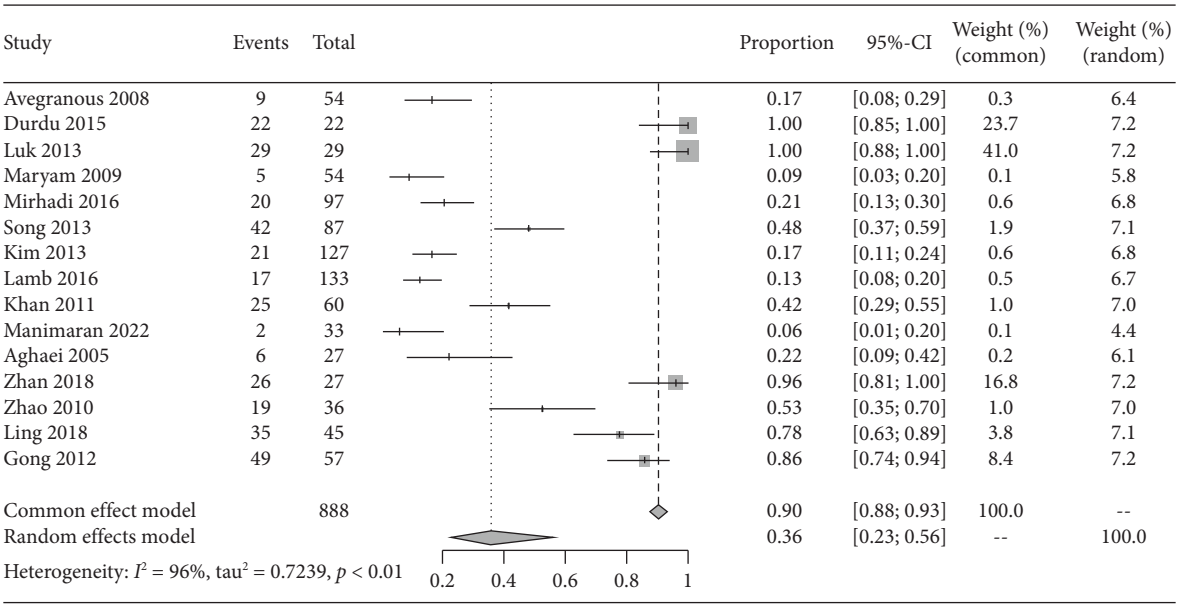

Figure 5: Incidence of mild contact dermatitis.

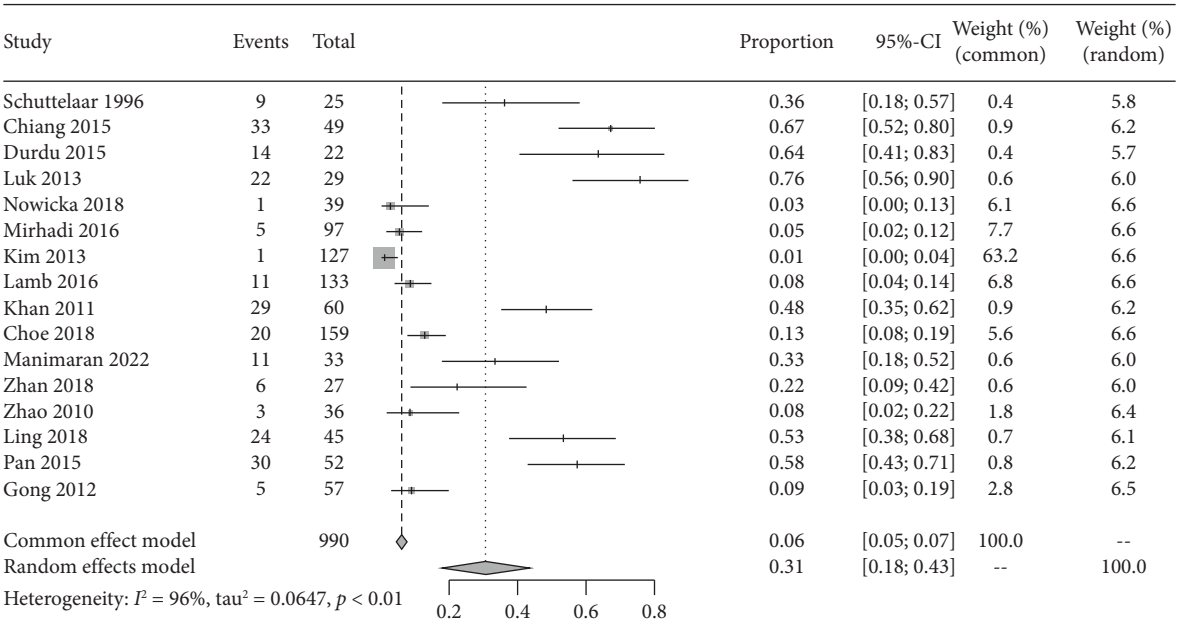

Figure 6: Incidence of severe contact dermatitis.

not be reported as an adverse effect in some studies. Due to the significant publication bias, estimates of the incidence of adverse effects may not be accurate. In addition to the adverse effects listed above, DPCP may cause some rare but serious side effects such as erythema multiforme major [14] and discoid lupus erythematosus [15] in some cases.

4.3. Recurrence Rate. AA can be a chronic relapsing disease. There is currently no treatment that can reduce the recurrence rate of AA. The recurrence rate of AA after DPCP treatment was approximately 37%. Few studies have reported the recurrence rate in patients with AT or AU. Therefore, subgroup analysis of these patients was not performed in this study. We recommend that future studies report the recurrence rate separately by the type of AA to determine whether the type of AA is associated with recurrence after treatment.

4.4. Mechanisms of Topical Immunotherapy. This study provided more sufficient evidence for the efficacy of DPCP in the treatment of AA. There are several hypotheses about the mechanisms of DPCP topical immunotherapy in the treatment of AA. From the perspective of skin lesions, antigen-presenting cells (APCs), $CD4^+$ T cells, and $CD8^+$

Study	Events	Total	Proportion	95%-CI	Weight (%) (common)	Weight (%) (random)
Chiang 2015	10	49	0.20	[0.10; 0.34]	4.4	5.9
Durdu 2015	10	22	0.45	[0.24; 0.68]	2.0	5.4
Luk 2013	16	29	0.55	[0.36; 0.74]	2.6	5.6
Maryam 2009	1	54	0.02	[0.00; 0.10]	4.9	5.9
Zawahry 2010	48	97	0.49	[0.39; 0.60]	8.8	6.1
Mirhadi 2016	3	97	0.03	[0.01; 0.09]	8.8	6.1
Kim 2013	1	127	0.01	[0.00; 0.04]	11.5	6.2
Lamb 2016	37	133	0.28	[0.20; 0.36]	12.0	6.2
Khan 2011	6	60	0.10	[0.04; 0.21]	5.4	6.0
Choe 2018	1	159	0.01	[0.00; 0.03]	14.4	6.2
Manimaran 2022	15	33	0.45	[0.28; 0.64]	3.0	5.7
Aghaei 2005	11	27	0.41	[0.22; 0.61]	2.4	5.6
Zhan 2018	5	27	0.19	[0.06; 0.38]	2.4	5.6
Zhao 2010	15	36	0.42	[0.26; 0.59]	3.3	5.8
Ling 2018	4	45	0.09	[0.02; 0.21]	4.1	5.9
Pan 2015	10	52	0.19	[0.10; 0.33]	4.7	5.9
Gong 2012	28	57	0.49	[0.36; 0.63]	5.2	6.0
Common effect model		1104	0.15	[0.13; 0.17]	100.0	--
Random effects model			0.22	[0.12; 0.33]	--	100.0
Heterogeneity: $I^2 = 95\%$, $\tau^2 = 0.0663$, $p < 0.01$						

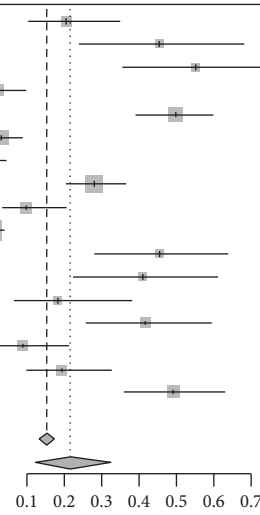

Figure 7: Incidence of lymphadenopathy.

Study	Events	Total	Proportion	95%-CI	Weight (%) (common)	Weight (%) (random)
Kutlubay 2020	3	98	0.03	[0.01; 0.09]	48.9	9.7
Durdu 2015	4	22	0.18	[0.05; 0.40]	2.2	7.6
Luk 2013	13	29	0.45	[0.26; 0.64]	1.7	7.1
Maryam 2009	4	54	0.07	[0.02; 0.18]	11.6	9.3
Khan 2011	5	60	0.08	[0.03; 0.18]	11.6	9.3
Manimaran 2022	5	33	0.15	[0.05; 0.32]	3.8	8.4
Aghaei 2005	5	27	0.19	[0.06; 0.38]	2.6	7.9
Zhan 2018	16	27	0.59	[0.39; 0.78]	1.7	7.0
Zhao 2010	8	36	0.22	[0.10; 0.39]	3.1	8.1
Ling 2018	6	45	0.13	[0.05; 0.27]	5.8	8.8
Pan 2015	19	52	0.37	[0.24; 0.51]	3.3	8.2
Gong 2012	20	57	0.35	[0.23; 0.49]	3.7	8.4
Common effect model		540	0.11	[0.08; 0.13]	100.0	--
Random effects model			0.22	[0.13; 0.31]	--	100.0
Heterogeneity: $I^2 = 89\%$, $\tau^2 = 0.0223$, $p < 0.01$						

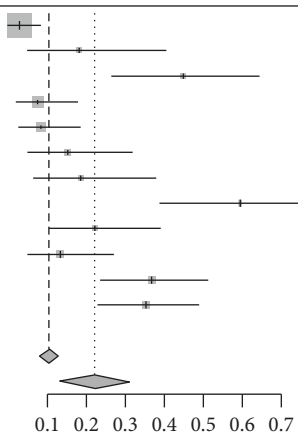

Figure 8: Incidence of hyperpigmentation.

Study	Events	Total	Proportion	95%-CI	Weight (%) (common)	Weight (%) (random)
Durdu 2015	5	22	0.23	[0.08; 0.45]	16.1	12.7
Luk 2013	1	29	0.03	[0.00; 0.18]	2.6	6.9
Zawahry 2010	2	97	0.02	[0.00; 0.07]	5.1	9.5
Mirhadi 2016	4	97	0.04	[0.01; 0.10]	10.4	11.7
Khan 2011	3	60	0.05	[0.01; 0.14]	7.9	10.9
Manimaran 2022	2	33	0.06	[0.01; 0.20]	5.3	9.6
Zhan 2018	10	27	0.37	[0.19; 0.58]	39.6	14.0
Zhao 2010	1	36	0.03	[0.00; 0.15]	2.6	6.9
Ling 2018	1	45	0.02	[0.00; 0.12]	2.5	6.9
Gong 2012	3	57	0.05	[0.01; 0.15]	7.9	10.9
Common effect model		503	0.13	[0.09; 0.17]	100.0	--
Random effects model			0.07	[0.03; 0.13]	--	100.0
Heterogeneity: $I^2 = 80\%$, $\tau^2 = 0.8258$, $p < 0.01$						

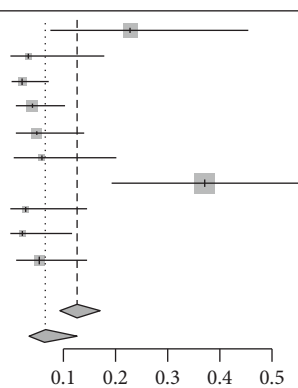

Figure 9: Incidence of hypopigmentation.

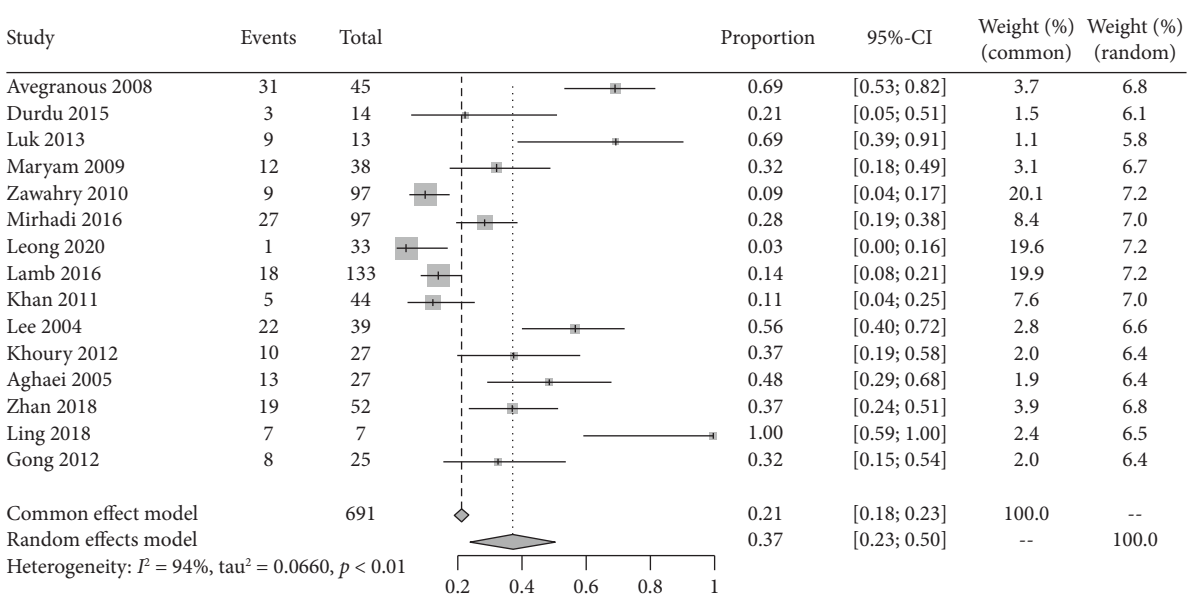

Figure 10: Recurrence rate.

T cells (among which $CD8^+NKG2D^+$ T cells may play a more important role) may infiltrate around the anagen hair follicles in active AA lesions. These cells recognize melanocyte- and keratinocyte-associated antigens and drive anagen hair follicles (especially anagen III/IV phase) into telogen [2]. DPCP can bind to endogenous epidermal proteins to form a complete antigen and induce allergic contact dermatitis in the epidermis, thereby interfering with the presentation of hair follicle antigens by APCs [8]. DPCP can also stimulate the infiltration of $CD4^+$ and $CD8^+$ T cells in the epidermis and induce the activation of suppressor T cells (such as Treg), thereby regulating the local inflammation of hair follicles [8]. From a systemic perspective, serum Th1 cytokines (such as IFN-γ and IL-12) and Th17 cytokines (such as Th17A and Th23) are elevated in patients with AA, which may provide a systemic inflammatory background and thus increase the susceptibility of hair follicles to autoimmune inflammation [16]. Gong et al. found that after DPCP treatment, serum levels of the Th1 cytokines IFN-γ and IL-12 decreased significantly in AA patients with a good response, while serum levels of the Th2 cytokines IL-4 and IL-10 increased dramatically. Therefore, it is speculated that DPCP treatment may inhibit the pathogenic effect of Th1-type responses on hair follicles by regulating the balance between Th1-type immune responses and Th2-type immune responses [17].

4.5. Protocol of DPCP Topical Immunotherapy. For the DPCP treatment protocol for AA, most studies in this meta-analysis were similar. First, the patients' scalp was sensitized with 2% solution of DPCP in acetone. The sensitization area was 2 cm ∗ 2 cm~4 cm ∗ 4 cm. The treatment started 2 weeks later. The application frequency was once a week to once every 2 weeks. The initial concentration was 0.001%. The concentration was then gradually increased until the patients developed allergic contact dermatitis. The concentration was then maintained. Light exposure and shampooing were avoided for 48 hours after application. However, there were differences in the maintenance treatment after that. Some studies simply discontinued the drug administration once the desired effect was achieved. Others gradually extended the dosing interval. As a result, the length of treatment varies from as little as 2 months to as long as 15 years. On average, however, it typically spans about 4–6 months. In addition, some studies suggested a stepwise approach to DPCP application, recommending its initial use on one side of the scalp, and proceeding to treat the other side only after observing positive effects on the first side. In most studies, DPCP was applied by physicians or nurses, but in two studies, it was applied by patients themselves at home, and these two studies found similar efficacy to hospital-based studies [18, 19].

5. Limitations

Due to language limitations, the literature search was conducted in English and Chinese databases only.

Most of the studies of DPCP in the treatment of AA were single-arm trials or retrospective analyses. There were only a few controlled trials, and the drugs used in the controlled groups were different. Therefore, the only outcome measure used was the regrowth rate. This may reduce the level of evidence and increase the heterogeneity.

Due to the different criteria used to assess hair regrowth in different studies, it was not possible to stratify the hair regrowth rate more precisely. In addition, because of the different focus of data collection in different studies, subgroup analysis of the incidence of adverse effects and recurrence rates in different types of AA could not be performed.

6. Conclusion

DPCP topical immunotherapy is an effective treatment for various types of AA, and most of its common side effects are acceptable. The response of different patients to DPCP topical immunotherapy is quite different, and the reason needs to be further clarified by conducting basic research on the pathogenesis of AA.

Abbreviations

AA: Alopecia areata
APCs: Antigen-presenting cells
AT: Alopecia universalis
AU: Alopecia totalis
DNCB: Dinitrochlorobenzene
DPCP: Diphenylcyclopropenone
MINORS: The methodological index for nonrandomized studies
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SADBE: Squaric acid dibutyl ester
SALT: Severity of Alopecia Tool.

Data Availability

All the data we used were collected from the following databases: PubMed, Embase, Cochrane Library, Sinomed, WanFang Data, and Chinese Medical Journal Network. The studies we included have been cited in supplements. The English literatures included in this article are available on the following websites: https://www.embase.com/search/quick, https://pubmed.ncbi.nlm.nih.gov/, https://www.cochrane.org/. The Chinese literatures included in this article are available on the following websites: https://www.wanfangdata.com.cn/index.html, https://www.sinomed.ac.cn/index.jsp, https://www.medjournals.cn/index.do.

Additional Points

Capsule Summary. (i) Although the treatment of alopecia areata has evolved rapidly, the options for treating alopecia areata are still limited. (ii) This systemic review and meta-analysis evaluated the efficacy, safety, and recurrence rate of diphenylcyclopropenone topical immunotherapy for alopecia areata. (iii) The overall rate of any hair regrowth after diphenylcyclopropenone treatment was 69% in patients with alopecia areata and 42% in patients with alopecia totalis or alopecia universalis. The overall rate of complete hair regrowth was 23%. (iv) Diphenylcyclopropenone topical immunotherapy is confirmed to be both safe and effective for the treatment of alopecia areata.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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Supplementary Materials

S1: studies included and citation. This supplement listed the studies included by our meta-analysis and cited these studies. S2: PRISMA checklist. This supplement listed the PRISMA checklist of our meta-analysis, which pointed out where each part of our meta-analysis located in the article. Supp Figures 1-10: supplementary figures. These supplements provides figures that do not appear in the main text, but are also important for explaining the conclusion of the article. (*Supplementary Materials*)

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