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REVIEW ARTICLES

A systematic review on the treatment of pediatric severe alopecia areata by topical immunotherapy or Anthralin (contact sensitization) or low-level light/laser therapy (LLLT): focus on efficacy, safety, treatment duration, recurrence, and follow-up based on clinical studies

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Abstract

Introduction: Alopecia areata (AA) in its extensive and severe forms is treatment-challenging, especially in pediatrics.

Method: A PRISMA-compliant systematic review of seven electronic databases was searched by the terms "alopecia areata," "pediatric," "topical immunotherapy," "Anthralin," and "light therapy" from inception until March 2021. All the alternative names of the disease and therapies have been included in the search terms. 790 articles went to title abstract review by two independent reviewers. In the subsequent level, a review of the full text of studies was conducted.

Results: Finally, 10 relevant articles in terms of content structure, subject coverage, and purpose, were selected for further review. The highest percentages of complete hair regrowth were 79.6% and 63.61% by SADBE (topical immunotherapy) and laser therapy. By Anthralin (contact sensitization), the complete response rate was below 50% (between 30 and 35%). Regarding average response, the most effective methods were local immunotherapy (with an average effectiveness of 53.8%), laser therapy (52.55%), and the use of Anthralin-induced contact dermatitis (30.86%), respectively. However, recurrence rate—after treatment with induced contact dermatitis by topical medications like Anthralin (contact sensitization)—was lower (mean 43.53%) in comparison with local immunotherapy (57%). In topical immunotherapy, light base therapy, and contact sensitization, the highest percentage of complete hair regrowth and the average response rate were (63.61% and 52.55%), (79.6% and 53.8%) and (32% and 30.8%), respectively. These methods are considered safe in children.

Conclusion: A high and more than 50% efficacy in hair regrowth could be expected by topical immunotherapy and light/laser therapy method. No serious side effects have been observed by these methods that are well tolerated in children. Therefore,

Abbreviations: AA, Alopecia Areata; DCPC, Diphenylcyclopropenone; LLLT, Low-level laser therapy; SADBE, Squaric acid dibutyl ester; UV, Ultraviolet.

a combination of local immunotherapy and light/laser therapy could be suggested for the treatment of extensive AA in children. The use of Anthralin could be associated with a lower but more durable response. These points are important for patient selection in individualized situations.

KEYWORDS
alopecia, contact sensitization, low-level light therapy, pediatric, topical immunotherapy

1 | INTRODUCTION

1.1 | Rationale

Alopecia areata (AA) is a chronic inflammatory disorder in which T-cell autoimmune attacks occur on hair follicles and sometimes nails (1). The disease, which initiates with acute hair loss, can appear in one or more spots with limited development, or it can be severe and progresses to AA totalis or AA universalis (2,3). AA, which is characterized by patchy areas, without sores, and hair loss, affects both adults and children and is one of the most common diagnoses in children, with approximately 20% of all cases occurring in children (4-6). It is also estimated that approximately 40.2% of patients show the first symptoms of the disease by the age of 20 (7). Most children with AA have a mild localized disease, affecting less than 50% of the scalp. AA in children is associated with atopy, nail changes such as twenty nail dystrophy syndrome, and positive family history (1). A variety of treatments are available for AA, including immunotherapy (such as topical, intravenous, or systemic corticosteroids), calcineurin inhibitors, contact sensitizers, or psoralen with UVA. However, most studies have been performed on adults with limited data in children (2,8). Managing AA in children is challenging due to their chronic condition (1). Assessing the effects of a disease on a child's physical and emotional health is of great importance, such as the effects on self-esteem and peer acceptance (1,9). Anxiety, frustration, guilt, and parental expectations should also be managed proactively to ensure overall patient management (1). Considering that severe and refractory AA initiates in childhood along with the importance of treatment in the pediatrics age group in terms of safety and tolerability, evaluation of AA treatment in children is greatly important, but there has always been a gap in previous studies in this field, and even some trials are not performed on children; thus, our data on AA in children, especially severe cases, are highly limited.

1.2 | Objective

This systematic review conduct on the treatment of pediatric severe alopecia areata (totalis, universalis, ophiasis diffuse patchy, or over 30%–50% of scalp area) by topical immunotherapy (Diphenylcyclopropenone or Diphencyprone or DCPC) or squaric acid dibutyl ester (SADBE) or Anthralin (contact sensitization) or low-level light/laser therapy (LLLT) with focus on efficacy, safety, treatment duration, recurrence, and follow-up based on clinical studies.

2 | MATERIALS AND METHODS

2.1 | Protocol and registration

This study is implemented according to the PRISMA statement(10). Figure 1 shows the PRISMA diagrams, the selection of reviewed articles.

2.2 | Eligibility criteria

The inclusion criteria contain all English cohort or clinical trials studies about the population under 18 years with any type of alopecia areata treated with topical immunotherapies (Diphenylcyclopropenone or Diphencyprone or DCPC) or squaric acid dibutyl ester (SADBE) or Anthralin (contact sensitizer or cignolin) or Low-Level Light / Laser therapy (LLLT) before March 16, 2021.

The exclusion criteria consisted of all publications not meeting the above, non-English literature, case reports, reviews, animal studies or laboratory studies, and studies in which another type of alopecia was reported, and studies not mentioning these types of therapies.

2.3 | Information sources

Databases PubMed (http://ncbi.nlm.nih.gov/pubmed), Scopus (http://WWW.scopus.com), Embase (http://WWW.embase.com), and Google Scholar (http://scholar.google.com), Web of Science (http://apps.lib.wosg.ir), ScienceDirect (https://www.sciencedirect.com), and Cochrane library (https://www.cochrane.org/) have been searched for the evidence.

2.4 | Search

Table 1 shows the search strategies used, designed mainly to not limit the entries to any condition. The search started and completed on March 16, 2021. Google Scholar, as a cumulative database, was limited only to the first 200 related results. The search was done with these keywords: "alopecia areata," "pediatric," "topical

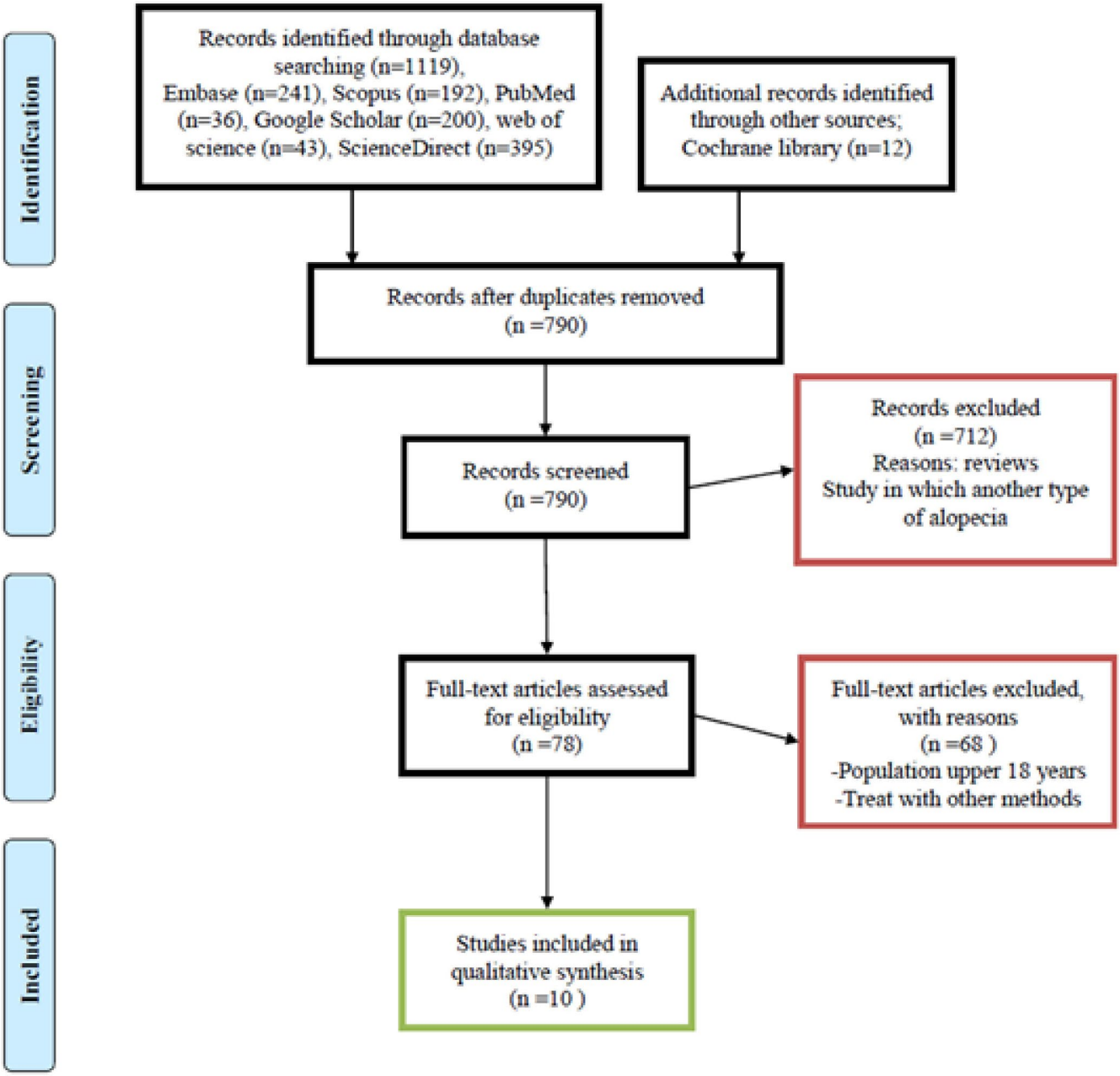

FIGURE 1 Diagram of the selection of reviewed articles.

immunotherapy," "Diphenylcyclopropenone," "squaric acid dibutyl ester," "Anthralin,""Cignolin" "light therapy," and "UV".

2.5 | Data collection process

The study's team members were of the high expertise. Endnote® X9 (Clarivate Analytics, Philadelphia, USA) was used for study screening and data extraction. Seven hundred and ninety articles were obtained from the mentioned databases. Two independent reviewers assigned each study to the inclusion and exclusion groups. In the first step, every member read the titles and abstracts, and if accepted, evaluated the full text. In the second step, the full text of 78 studies was reviewed, and the final inclusion process was executed by evaluating of different aspects of methodology, including sampling methods, reliability of the tools used, and the objectives of the study. Disagreement situations regarding the inclusion process were resolved by a third expert reviewer. Finally, 10 articles were selected for data extraction.

3 | RESULTS

3.1 | Study characteristics

The results were systematically reviewed in Table 2. Based on the data extracted from Table 2, the total number of patients in 10

TABLE 1 Search Strategies (Sentences Searched in Databases).

Search strategies (Sentences Searched in Databases	
PubMed	("alopecia areata" OR "totalis" OR "universalis" OR "ophiasis" OR "diffuse patchy") AND ("pediatric" OR "children") AND ("topical immunotherapy " OR "Diphenylcyclopropenone" OR "Diphencyprone" OR "DCPC" OR "squaric acid dibutyl ester" OR "SADBE" OR "Anthralin" OR "light therapy " OR "UV" OR "LLLT")
Google Scholar	"alopecia areata" AND ("pediatric" OR "children") AND ("topical immunotherapy " OR "Diphenylcyclopropenone" OR "Diphencyprone" OR "squaric acid dibutyl ester" OR "Anthralin" OR "light therapy")
Scopus	TITLE-ABS-KEY (("alopecia areata" OR "totalis" OR "universalis" OR "ophiasis" OR "diffuse patchy") AND ("pediatric" OR "children") AND ("topical immunotherapy "OR "Diphenylcyclopropenone" OR "Diphencyprone" OR "DCPC" OR "squaric acid dibutyl ester" OR "SADBE" OR "Anthralin" OR "light therapy "))
Embase	("alopecia areata"/exp OR "allopeciaareatamaligna" OR "alopecia areata" OR "alopecia circumscripta" OR "area celsi" OR "areate alopecia") AND ("child"/exp OR "child" OR "children") AND ("immunotherapy"/exp OR "brm therapy" OR "biologic response modifier therapy" OR "biological response modifier therapy" OR "immune therapy" OR "immunogenic therapy" OR "immunoglobulin therapy" OR "immunological therapy" OR "immunological treatment" OR "immunomodulant therapy" OR "immunomodulary therapy" OR "immunomodulating therapy" OR "immunomodulation therapy" OR "immunomodulative therapy" OR "immunomodulator therapy" OR "immunomodulatory intervention" OR "immunomodulatory therapy" OR "immunomoduling therapy" OR "immunomodurating therapy" OR "immunotherapy" OR "phototherapy"/exp OR "light therapy" OR "phototherapy" OR "dithranol"/exp OR "1, 8 dihydroxy 9 (10h) anthracenone" OR "1, 8 dihydroxy 9 anthrone" OR "1, 8 dihydroxyanthranol" OR "1, 8 dihydroxyanthranole" OR "1, 8 dihydroxyanthrone" OR "1, 8, 9 anthracenetriol" OR "1, 8, 9 anthratriol" OR "1, 8, 9 trihydroxyanthracene" OR "a-fil" OR "amitase" OR "anthra-derm" OR "anthraderm" OR "anthraforte 1" OR "anthralin" OR "anthraline" OR "anthramed" OR "anthranol" OR "anthranol 0.1" OR "anthranol 0.2" OR "anthranol 0.4" OR "anthrascalp" OR "antraderm" OR "cignaethyl" OR "cignolin" OR "cignoline" OR "cigthranol" OR "cognolinbrown" OR "cygnolin" OR "derobin" OR "desmoline" OR "dioxyanthanol" OR "dioxyanthranol" OR "dithranol" OR "dithranol-hermal" OR "dithro" OR "dithrocream" OR "dithrocreme" OR "ditranol" OR "ditrastick" OR "drithocreme" OR "filorose" OR "lasan" OR "micanol" OR "psoradrate" OR "psorex" OR "psoriacide" OR "psoriatec" OR "psoricream" OR "psorinol")
Web of Science	ALL FIELDS: (("alopecia areata" OR "totalis" OR "universalis" OR "ophiasis" OR "diffuse patchy") AND ("pediatric" OR "children") AND ("topical immunotherapy "OR "Diphenylcyclopropenone" OR "Diphencyprone" OR "DCPC" OR "squaric acid dibutyl ester" OR "SADBE" OR "Anthralin" OR "light therapy "OR "UV" OR "LLLT")) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC.
Science Direct	("alopecia areata") AND ("pediatric" OR "children") AND ("topical immunotherapy " OR "Diphenylcyclopropenone" OR "Diphencyprone" OR "squaric acid dibutyl ester" OR "Anthralin" OR "light therapy")
cochrane	("alopecia areata" OR "totalis" OR "universalis" OR "ophiasis" OR "diffuse patchy") AND ("pediatric" OR "children") AND ("topical immunotherapy " OR "Diphenylcyclopropenone" OR "Diphencyprone" OR "DCPC" OR "squaric acid dibutyl ester" OR "SADBE" OR "Anthralin" OR "light therapy " OR "UV" OR "LLLT") in Title Abstract Keyword

articles (5,9,11-18) was 329, of which 91 were boys and 90 were girls (in 2 articles, the number of girls and boys was not reported). The mean age of the patients was 9.32 years (in one article the age of the patients was reported as less than 15 years). The types of Alopecia Areata reported in these articles included totalis, universalis, multilocular, subtotal, and ophiasis. In this study, a total of 10 original articles that were clinical studies were reviewed, of which 3 articles were retrospective study (30%), one prospective study (10%), one randomized blind study (10%), one article was Open-Label Study (10%), and one article was Cohort comprised study (10%). In three articles, the type of study was not reported.

3.2 | Results of individual studies

The most commonly used treatments in the reviewed articles were SADBE (30%) followed by laser therapy (20%), Anthralin (20%), Clobetasol and Hydrocortisone (10%), methotrexate (10%), and tofacitinib (10%), respectively. A study that used all treatments demonstrated that the mean duration of disease in patients was 4.21 years (this period was not reported in four articles), and the mean follow-up period was 2.48 years. The most reported side effects were mild erythema, pruritus, contact dermatitis, and hyperpigmentation. Recurrence after treatment was reported in four articles (40%) (treatments with SADBE, methotrexate, and Anthralin), and no recurrence was reported in other articles. In all the articles (100%), no serious side effects were reported, and the observed side effects disappeared after a while. Also, tolerability of the treatment by children was reported in three articles (30%) in which SADBE topical treatment and laser therapy (308-nm excimer lamp) were used. The lowest concentration and dosage used for SADBE treatment was 1% and the highest dosage was 3%. In this treatment, different doses were used once a week to once every two weeks. In the topical method, clobetasol was used twice a day for 2 periods of 6 weeks, Anthralin (contact sensitizer) was used twice a week for 5 minutes and methotrexate was used weekly. In laser treatment using a 308-nm excimer lamp, the minimum intensity used was 50 MJ/cm^2 and in the absence of side effects, the used intensity was higher. In these studies, the number of treatment sessions was twice a week for 3 months. Based on the data extracted from the present systematic

TABLE 2 Summary of the results obtained from the reviewed articles.

Author(s)/ year/	type of study	Title	study population / age / method	Dosage/ duration of use	Summary of results / side effects
Topical immunotherapy group					
Tosti et al, 1996	not mentioned	Long-term results of topical immunotherapy in children with alopecia totalis or alopecia universalis	33 children (20 boys and 13 girls) aged between 6 and 14 years 10 of them had alopecia areatatotalis and 23 of them had alopecia areatauniversalis. These patients received topical treatment with SADBE. The average duration of their disease was 4.7 years. All previous treatments were stopped at least 6 months before the start of immunotherapy.	After 3 weeks, SADBE was used once a week. Concentrations were selected to maintain mild contact dermatitis. These concentrations ranged from 0.00001% to 1%, depending on the patient's response. Treatment was continued in all patients for at least one year. For patients with complete hair regrowth, treatment was continued for at least 1 year after regrowth, with the exception of one patient who stopped using SADBE, 3 months after regrowth. Treatment was not discontinued in patients with small patches of hair loss during the follow-up period The follow-up period was 4 to 12 years (mean 5.9 years).	Complete hair regrowth was observed in 10 of 33 children (30.3%). In 6 of the 33 patients, sporadic regrowth occurred without any cosmetic improvement in their alopecia. In these patients, topical immunotherapy was discontinued after 1 year. Patients who responded to treatment were not statistically different in terms of sex, age, or associated diseases, compared with patients with minimal regrowth or those with non-pigmented vellus hair regrowth. The presence of antibodies and family history of AA were less frequent in children who had complete regrowth than in other children. Seven out of 10 children with complete hair regrowth had a recurrence during the follow-up period. Each of the seven had several areas of AA, which accounted for more than 60% of cases. Recurrence of the disease was observed 1 month to 3 years after hair regrowth and all children were treated due to the presence of several small areas (<2 cm) of alopecia at the time of recurrence. In all of these patients, prolonged treatment failed to induce full hair regrowth. Therefore, treatment was stopped 6 months to 1 year after the onset of recurrence. We observed mild recurrence in the remaining three patients during the follow-up period. In these patients, recurrence occurred 4 to 21 months after full regrowth. Topical immunotherapy was discontinued 1 to 3 months before the onset of recurrence. All patients had a few (<5) small areas of alopecia that did not cause cosmetic problems and were well controlled after SADBE treatment. The mean follow-up of these 3 patients was 10 years. Two patients have maintained complete hair regrowth, although SADBE treatment has been discontinued for 2 years. Topical immunotherapy was well tolerated in all our patients. Only one child had severe contact dermatitis that required temporary discontinuation of treatment. Swollen lymph nodes were observed in nine children.

(Continues)

TABLE 2 (Continued)

Author(s)/ year/	type of study	Title	study population / age / method	Dosage/ duration of use	Summary of results / side effects
DALL'OGLIO et al, 2005	open-label, paired-comparison, clinical trial	Topical immunomodulator therapy with squaric acid dibutylester (SADBE) is effective treatment for severe alopecia areata (AA): Results of an open-label, paired-comparison, clinical trial	263 patients (139 females and 124 males) of which 97 were children (mean age of children was 7.59 years) Diagnosed with severe AA (affecting more than 40% of the scalp) These patients were treated with squaric acid dibutylester (SADBE) The treatment group included patients with patchy alopecia (PA; 26), alopecia ophiasis (AO; five), alopecia totalis (AT; 14), and alopecia universalis (AU; no patient). The mean duration of the disease was 3.5 years. Follow-up period 2 to 8 years	Sensitization was performed topically using 3% SADBE directly on the scalp on a hairless patch or in diffuse alopecia, on one side of the head. After 2 weeks, serial dilutions (0.0003%, 0.003%, 0.03%, 0.3%, and maximum 3%) were applied to the scalp to identify the minimum concentration capable of causing the eczema response. SADBE treatment was then performed weekly using a more appropriate dilution as indicated by the patch test. The use of topical corticosteroids was avoided to minimize the confounding effects. When hair regrowth was maintained for 3 months, a gradual reduction was performed for the topical dose SADBE, that is, the treatment was performed every 2 weeks for 3 months, followed by once every 3 weeks for 3 months. Thereafter, monthly SADBE programs were performed for 6 months before complete cessation of treatment. During follow-up, all patients were re-evaluated clinically every 2 months, and in case of recurrence for at least 2 years.	At the end of treatment, 43 patients (79.6%) achieved full regrowth, after an average treatment period of 34.5 weeks in 73% of adults and 28 weeks in 100% of children. In the control group, during the same period, complete regrowth was observed in 27 patients (50%). A statistically significant improvement was observed in treated patients compared to controls. In the treatment group, 24 patients (44%), including 18 patients with PA (75%), one patient with AO (4%), one patient with AT (12.5%), and one patient with AU (4%) experienced recurrence, and in the control group 28 patients (52%) experienced recurrence of the disease. The recurrence in the treatment group was mild in all patients, but in three patients (one PA, one AO, one AT), small patches formed that were easily controlled with local stimulants. On the other hand, in the control group, all recurrences were severe. The time of recurrence after treatment was not reported.
Sakai et al, 2019	retrospective cohort study	Effect of topical immunotherapy with squaric acid dibutylester for alopecia areata in Japanese patients	60 patients were children under 15 years old and 33 patients were over 16 years old The average duration of AA was 71 months	Sensitization was performed using 1% SADBE on the hairless area for 24 to 48 hours. Two weeks later, after Sensitization confirmation, a patch test was performed with 0.1%, 0.01%, 0.001%, 0.0001% and 0.00001% of SADBE. Forty-eight hours after the patch test, the minimum erythema concentration was determined and 0.1 of the SADBE concentration was applied for the first time. Patients were told to return to the outpatient clinic to confirm whether they had any serious side effects such as itching or contact dermatitis in the treated area. If mild itching persisted for 2 to 3 days, the used concentration was considered appropriate and was applied once every 1 or 2 weeks. In case of persistent itching lasting for 3 or more days or a severe eczema reaction, the SADBE concentration decreased and the appropriate concentration was reassessed 1 to 2 weeks later. 6 months after starting local immunotherapy, the area of hair loss was assessed. Follow-up was performed for one year.	6 months after the first use of SADBE in 5 patients with more than 25% hair loss, 2 patients were improved from the disease, and 3 patients retained their disease. Out of 8 patients with hair loss between 25%–49%, 1 was improved from the disease, 2 retained the disease, and 1 got worse. Among 13 people with hair loss between 50%–74%, in 7 people the hair loss was reduced (more than 25%), 3 people retained their disease and 1 person got worse. In 7 patients with hair loss between 99%–75%, 2 patients had a decrease in hair loss (25%–49%), 2 patients had a reduction to 50%–74%, and 3 patients retained their disease. The overall response of patients to severe AA after one year was 51.5%. Recurrences after treatment and side effects were not reported.

(Continues)

TABLE 2 (Continued)

Author(s)/ year/	type of study	Title	study population / age / method	Dosage/ duration of use	Summary of results / side effects
Light-based therapy group					
AL-MUTAIRI, 2007	not mentioned	308-nm Excimer Laser for the Treatment of Alopecia Areata	18 patients (4 children and 14 adults) with 42 recalcitrant patches who did not respond to various treatments for AA, were enrolled in this study. The mean age of children (2 girls and 2 boys) was 9.5 years. The mean duration of this disease in studied children was 15 months. Follow-up period was 6 months	The laser used was a 308-nm excimer laser. Before starting treatment, the minimum dose of erythema was determined on the skin of the arm. Each lesion was treated twice a week for a maximum of 24 sessions (more than 3 months). The initial infiltration rate of 50 mJ / m2 was less than the minimum erythema dose. Then the infiltration rate of both sessions increased by 50 mJ / cm2. At the last visit, patients' opinions about the effectiveness of treatment and their level of satisfaction (excellent, good, average, poor) were recorded. Clinical evaluation was performed before treatment, every 2 weeks during the 3-month treatment period, and 6 months after treatment discontinuation. Patients who did not have complete hair regrowth at the end of 3 months were reported as non-respondent.	Hair regrowth was observed in 17 patches (41.5%). No hair regrowth was observed in control patches. Regrowth was observed in the second month in 12 patients. Four lesions (3 in children and 1 in adults) that did not show hair regrowth, were all present in patients with atopic diathesis (bronchial asthma). Only one adult patient with alopecia totalis did not respond to treatment. Side effects observed in different patients were limited to mild erythema, hyperpigmentation, itching, and mild peeling of the skin. The tolerance of this treatment by patients was excellent. Recurrence was not reported after treatment.
Al-Mutairi, 2009	cohort comprised study	308-nm Excimer Laser for the Treatment of Alopecia Areata in Children	11pediatric patients (7 boys and 4 girls) with a mean age of 7.4 years with 30 recalcitrant patches	The laser used was the Excimer 308-nm laser. Before starting treatment, the minimum erythema dose (MED) was determined on the skin of the arm. Each lesion was treated twice a week for a maximum of 24 sessions. The initial flow was 50 mJ⁄cm2 less than MED. After that, in both sessions, it was increased by 50 mJ⁄cm2. Patients' and parents' opinions about the effectiveness of treatment and satisfaction (excellent, good, average, and poor) were recorded. Clinical evaluation was performed before treatment, every 2 weeks during the 3-month treatment period, and 6 months after treatment discontinuation. Patients who did not have complete hair regrowth at the end of 3 months were reported as non-respondent. the follow-up period was 6 months	Hair regrowth was observed in 18 of 30 patches (60%). No hair regrowth was observed in control patches. Hair regrowth was observed in eight patients in the second month. A total of 22 scalp lesions, including two patients with alopecia totalis, were studied. Of these, 14 lesions (63.6%) showed complete regrowth. Four lesions (including two children with alopecia totalis) that did not show hair regrowth were all present in patients with atopic diathesis. Side effects observed in different patients were limited to mild erythema, hyperpigmentation, itching, and mild peeling of the skin. The laser treatment tolerability was excellent. Recurrence was not reported after treatment.

(Continues)

TABLE 2 (Continued)

Author(s)/ year/	type of study	Title	study population / age / method	Dosage/ duration of use	Summary of results / side effects
Use of contact sensitization topical medications					
Royer et al, 2011	retrospective study	Efficacy and tolerability of methotrexate in severe childhood alopecia areata	14 children (8 girls and 6 boys) with an average age of 9 years The average duration of AA was 5.7 years Not all patients responded to routine therapies including topical agents (corticosteroids, tacrolimus, minoxidil), ultraviolet A (UVA), isoprinosine, or oral corticosteroids.	The mean dose of methotrexate (MTX) was 18.9 mg weekly. Corticosteroids were administered with MTX in eight of 14 patients (54%) (oral prednisone or prednisolone 0.5 to 1 mg/kg) once daily for 1–2 months, and for six patients (four in the baseline and two in the middle of treatment with MTX) initial methylprednisolone pulse was given(300 or 500 mg daily for 3 months for the remaining two patients). The fifth patient received three intralesional corticosteroid injections for two resistant ophiasis patches. The mean duration of treatment was 14.2 months.	One of 14 children could not be evaluated because the treatment was not tolerated and MTX was stopped after 1 month. Out of 13 evaluable children, there were five treatment successes (77%–99% regrowth in four patients and 50%–74% regrowth in one patient). These five children responded to treatment with an average time of 4.4 months. Of the five respondents, one stopped MTX after 31 months and had no recurrence 17 months after stopping treatment, and the other four had no recurrence for 16 months. The treatment failed in the remaining eight children. Three patients had recurrence after initial regrowth (two recurrences during treatment and one recurrence 4 months after MTX discontinuation). No serious side effects were reported. Limited Herpes zoster was observed in one patient receiving systemic corticosteroids. Nausea was reported in one patient on the day of MTX administration.
Lenane et al, 2014	randomized, blind, 2-arm, parallel group, superiority trial	Clobetasol Propionate, 0.05%, vs Hydrocortisone, 1%, for Alopecia Areata in Children A Randomized Clinical Trial	42 patients with a mean age of 7.3 years (23 girls and 19 boys) These patients had alopecia areata and at least 10% of their scalp was affected. 5 patients had a family history of this disease. 8 patients had never been treated before starting the study, and the rest had received a variety of medications, including topical, oral, and intramuscular corticosteroids.	Patients used clobetasol propionate 0.05% or hydrocortisone 1%. Patients were instructed to apply a thin layer of the cream in areas of hair loss twice a day for 2 periods of 6 weeks, with 6 weeks of rest (a total of 24 weeks). Every week, patients were given identical 50-gram jars containing creams with similar texture, color, and odor.	The reduction in hair loss was greater in the group of patients treated with clobetasol propionate compared to the hydrocortisone group. The percentage of reduction in hair loss at 24th week was higher than the initial stage in the clobetasol group (96.5%; interquartile range of 64% to 100%) compared with the hydrocortisone group (14.6%; interquartile range of 44.3% to 80.8%). At week 24, seventeen children in the clobetasol group (85%) had at least a 50% reduction in hair loss compared to 7 of 21 children in the hydrocortisone group (33.3%). None of the patients complained of burning when using the cream. Recurrence was not reported after treatment.

(Continues)

TABLE 2 (Continued)

Author(s)/ year/	type of study	Title	study population / age / method	Dosage/ duration of use	Summary of results / side effects
Ozdemir and Balevi, 2015	Prospective study	Bilateral Half-Head Comparison of 1% Anthralin Ointment in Children with Alopecia Areata	30 children (17 girls and 13 boys) with chronic, severe, and widespread AA who had not received any treatment for at least 1 month prior to the study. The mean age of the patients was 14.1 years (between 17–17 years). 46.7% of patients had multilocular AA (MLA), 43.3% had subtotal AA (AST), 6.7% of them had alopecia universalis (AU) and 3.3% had alopecia totalis (AT). AA severity and patients' clinical response were measured using the severity of alopecia tool (SALT). At the first visit, patients were physically evaluated to determine the percentage of scalp involvement and type AA. At subsequent visits, the side effects of anthralin treatment were recorded based on physical examination and patient reports. Patients were treated with anthralin for 3 years.	1% anthralin in petrolatum was used as a short contact treatment in alopecia areas in the left half of the scalp. The contact time was initially 20 to 30 minutes per day and increased to 10 minutes every 2 weeks and increased to a maximum of 1 hour or until the onset of low-grade dermatitis. Areas of alopecia on the right side of the scalp were not treated to be evaluated as a control after 1 year. After the baseline visit (month zero), patients returned to the clinic, every 3 months in the first year, for evaluation based on SALT assessment and treatment safety assessment. At the end of the year, patients who did not require any further treatment were considered complete respondents. Partial respondents continued treatment until the end of 2 years. For patients who initially achieved a 50% reduction in pre-treatment SALT score (SALT50), the total SALT50 score was reassessed for the entire scalp at the end of the first year. After the first year, patients were evaluated every 6 months. After the second year, patients returned to the clinic for follow-up at 6-month intervals and in these visits, evaluation of the effectiveness and safety of the treatment was performed.	During the first 12 months, 10 patients (33.4%) had a complete response to treatment, of which 2 patients (20%) within 6 months, 5 patients (50%) during 9 months, and 3 patients (30%) within 12 months, completely responded to the treatment. Eleven patients (26.6%) had a relative response within 12 months. The number of patients who scored SALT50, SALT75, or complete response increased by the end of month 12. The mean time of the first and maximum response in terms of new hair growth was 3 and 9 months, respectively. All patients had irritation and itching around the treated areas. Cervical lymphadenopathy was observed in all patients and temporary hyperpigmentation occurred in other parts of the body due to contact with anthralin in seven patients (23.3%). No serious side effects were observed in the patients. Recurrence was not reported after treatment.
Wu et al, 2018	retrospective study	Treatment of pediatric alopecia areata with anthralin: A retrospective study of 37 patients	37patients with a mean age of 9 years (22 boys and 15 girls) with AA and the types of disease were Patchy, Ophiasis, Totalis, and Universalis.	These patients used 0.5% anthralin cream daily for 5 minutes, and 1% anthralin cream for 30 minutes twice a week. 2 patients used 1% anthralin shampoo daily instead of cream. The response to treatment was measured using the SALT tool. The mean follow-up period was 2.5 years.	Twelve patients (32%) experienced complete hair regrowth, while 25 patients (68%) experienced at least 50% hair regrowth using anthralin. In patients with at least 50% hair regrowth, the mean time of the first clinically observed response was 3.4 months, and the mean time of maximum response was 15 months. Four patients stopped the use of anthralin due to skin irritation. Recurrence occurred in 64% of people with at least 50% hair regrowth. The time of recurrence after treatment was not reported.
Putterman and Castelo-Soccio, 2018	not mentioned	Topical 2% tofacitinib for children with alopecia areata, alopecia totalis, and alopecia universalis	11 patients aged 4 to 16 years (8 girls and 3 boys) with AA, AT, or AU Previous treatments included the use of prednisone, oral methotrexate, and topical steroids.	These patients were treated with topical 2% tofacitinib formulation.	The mean change in score of Severity of Alopecia Tool (SALT) was a 32.3% reduction. Eight of the 11 patients showed an improvement in the SALT score. Three patients had hair regrowth (27.27%). All patients tolerated the treatment without side effects. Irritation in the treated area was reported in one patient. Recurrence was not reported after treatment.

review, the highest percentages of complete hair regrowth were 79.6% and 63.61%, which were related to the use of SADBE and laser therapy, respectively. Complete hair regrowth was also reported in 33.4% and 22% of patients treated with Anthralin and tofacitinib, respectively. On the other hand, in the articles related to laser treatment, the highest percentage of complete hair regrowth was 63.61%. Also, in another article related to this treatment, complete regrowth in a large area, without recurrence and complication, was reported. In an article on the use of MTX, 77%–99% regrowth was reported in 30.76% of patients treated with methotrexate. In a study on the topical use of tofacitinib, hair regrowth was observed in 27.27% of patients. In another article, the topical use of Clobetasol and Hydrocortisone for the treatment of Alopecia Areata was compared. The results of this study showed that Clobetasol reduces the level of hair loss by 96.5%, in comparison with hydrocortisone that induced a 14.6% reduction.

3.3 | Topical immunotherapy group

In 30% of the articles, local immunotherapy was evaluated. The highest percentage of complete hair regrowth and the mean response in this treatment group were 79.6% and 53.8%, respectively. During the follow-up period (with an average of 3.96 years) in this group, recurrence after treatment was reported in 66.66% of studies (2 of 3 articles) and it was not reported in one article. In one article, 44% of patients treated with SADBE had a recurrence, and in another article, 7 of 10 people with complete hair regrowth experienced a recurrence within one month to 3 years after treatment, and in other 3 patients, mild recurrence was observed within 4 to 21 months after treatment. The mean recurrence rate in this treatment group was 57%. These studies demonstrated that this treatment was tolerable in this group of patients. In addition, in 66.66% of these articles, no side effects were reported and in one article, there were mild side effects (such as contact dermatitis), which resolved with discontinuation of treatment.

3.4 | Light-based therapy group

Light-based therapy was reviewed in 20% of the articles. The highest percentage of complete hair regrowth and the mean response in this treatment group were 63.61% and 52.55%, respectively. The mean follow-up period in this treatment group was 6 months, during which there was no report of the recurrence. Both articles reported that this treatment was well tolerated by children. Mild side effects (such as mild erythema and pruritus) were reported in both articles.

3.5 | Contact sensitizer topical medications

In 50% of the articles, the use of contact sensitizer (Anthralin) was evaluated. The highest percentage of complete hair regrowth and the average response in this treatment group was 32% (using Anthralin) and 30.86%, respectively. The rate of hair regrowth in this treatment group (in 3 articles, 60%) was below 50%, although 77%–99% regrowth was also reported in 30.76% of patients treated with methotrexate. The mean follow-up period in this treatment group was 2.25 years, during which the recurrence was reported after treatment in two articles (40%). In one article, the recurrence occurred for two people during the treatment period and one person 4 months after the cessation of treatment, and in another article, the recurrence time was not reported. The mean recurrence rate in this treatment group was 43.53%. Side effects (skin irritation in the treatment area, itching) were also mild and tolerable in this treatment group.

4 | DISCUSSION

4.1 | Mechanism of action

Potential autoimmune mechanisms involved in the pathogenesis of AA include sensitization of T lymphocytes, particularly CD8+ T cells, to follicular antigens. Activation of the lymphocytes, composing the perifollicular infiltrate characteristic of AA, induces the release of several Th1 cytokines—interleukin (IL)-1 alpha, IL-1 beta, and tumor necrosis factor (TNF) alpha—capable of inhibiting hair follicle growth and arresting hair synthesis, with early termination of anagen (19-21).

4.1.1 | Topical Immunotherapy Mechanism

There are various theories on the mechanisms of immunotherapy for the treatment of AA. The main mechanism focuses on antigenic competition using immunomodulators to induce allergic contact dermatitis at the applied area through delay-type hypersensitivity (22). The Allophycocyanins (APC) detects the complex of the substance binding endogenous protein and activates antigen-specific T cells, causing the clinical condition of dermatitis (23). With the elicitation of an allergic reaction, suppress T cells infiltrate around hair follicles in the late phase. These newly infiltrating T cells act against the autonomous CD4+ and CD8+ T-cell populations and disturb APC migration at the affected follicles. A decrease in CD4+ T cells and increase in CD8+ T cells in the treated area result in an alteration of lymphocyte perifollicular pattern, with a decrease in the ratio of CD4+ to CD8+ T cells from 4:1 to 1:1. Also, MHC class I and II expression declines after treatment with topical immunotherapy, which in turn can induce the expression of immunoregulatory molecules, such as cytotoxic T-lymphocyte-associated protein 4, forkhead box P3, and indoleamine 2,3-dioxygenase (24). Hence, improvement of local immunoregulation can promote hair regrowth in AA (22). Another mechanism regarding cytokine alteration has also been proposed. Th1 cytokines, such as IL-1β, IFN-γ, and IL-2, were elevated in untreated AA. However, after receiving treatment with topical immunotherapy, levels of IL-12, IFN-γ, and Th17 cytokines reduced,

as well as increasing in regulatory cytokines, namely IL-2, IL-4, IL-8, and IL-10, and tumor necrosis factor (TNF)-α, in both serum and scalp biopsy specimens (25,26). The use of DPCP to increase mRNA expression of IL-2, IL-8, IL-10, and TNF-α was demonstrated. IL-10 is a key factor for the effectiveness of immunotherapy by inhibiting T lymphocytes (27,28). In conclusion, there are two possible mechanisms of topical immunotherapy in the treatment of AA. The first mechanism involves antigenic competition, which shifts the target of T cells from hair follicles to the epidermis. The second mechanism involves cytokine alteration, which increases in T-regulatory lymphocytes, causing the decline of follicular immune reaction. However, both mechanisms require further evidence to establish their roles in the treatment of AA.

4.1.2 | Light-based therapy Mechanism

Macrophage lineage cells have a high ability to coordinate both in terms of phenotype and function to maintain the tissue homeostasis. Macrophages can be activated by LPS or IFN-γ to an M1 phenotype that expresses pro-inflammatory cytokines and can kill microbial cells. Also, macrophages can be activated by IL-4/IL-13 to an M2 phenotype for phagocytosis of debris and tissue repair. Recent studies show that the M1 phenotype is often accompanied by a shift from oxidative phosphorylation to aerobic glycolysis for energy production (29). The laser therapy can activate the mitochondrial metabolism toward oxidative phosphorylation, and away from aerobic glycolysis. This is a plausible reason why laser therapy may change the macrophage phenotype from M1 toward M2 (30,31).

4.1.3 | Mechanism of contact sensitization

Anthralin

Anthralin is another option for topical immunotherapy, which induces irritant local dermatitis. The mechanism of action of Anthralin is associated with modulating the expression of cytokines (32).

Clobetasol and Hydrocortisone

Clobetasol propionate exerts its effect by binding to cytoplasmic glucocorticoid receptors and subsequently activates glucocorticoid receptor-mediated gene expression, resulting in synthesis of certain anti-inflammatory proteins while inhibiting the synthesis of certain inflammatory mediators. Specifically, clobetasol propionate appears to induce phospholipase A2 inhibitory proteins, thereby controlling the release of the inflammatory precursor arachidonic acid from membrane phospholipids by phospholipase A2.

Methotrexate

MTX is known to inhibit the enzyme dihydrofolate reductase, which leads to a decrease in intracellular reduced folate concentrations. This decrease inhibits purine and pyrimidine metabolism and nucleic acid synthesis consequently, resulting in antineoplastic effects when administered at high doses (15). MTX polyglutamates also inhibit AICAR (5-aminoimidazole-4-carboxamide ribonucleotide formyl transferase), an enzyme involved in purine synthesis, which finally leads to a buildup of adenosine, a mediator of many anti-inflammatory effects of MTX. Adenosine is released into the extracellular space, and—among multiple anti-inflammatory actions—inhibits white blood cell accumulation, leads to a reduction in TNF-α and IFN-γ synthesis, and inhibits a variety of monocyte, macrophage, and T-cell activities (33).

4.2 | Adverse effects:

4.2.1 | Topical immunotherapy group

SADBE

The most common adverse effect of topical immunomodulatory therapy is eczema, and other rare forms include local irritation, blister formation, persistent dermatitis, lymphadenopathy, generalized eczema, urticarial reaction, and vitiliginous depigmentation (34). In the studies on children population in our systematic review, 1 severe contact dermatitis and 9 swollen lymph nodes were observed as adverse effects (11).

DPCP

The most commonly encountered side effects are erythema and itching, followed by the formation of papules, vesicles, bullae, and flu-like symptoms. Other less frequent side effects are fever, general malaise, lymph node enlargement, irreversible hyperpigmentation of the head and neck, and vitiligo macules (35). The use of DPCP in children is still a controversial area. In 10 selected studies, side effects from DPCP were not mentioned, although some studies have shown good results with acceptable side effect profiles (36). In 2020, a study conducted by Kutlubay, children over 5 years of age were also included and the treatment results or safety parameters were similar to those of the adult patients (37).

4.2.2 | Light-based therapy group

Possible adverse events of laser therapy are burn, persistent erythema, and pain. In different studies, the adverse events were mild for children, including erythema, hyperpigmentation, itching, and mild peeling of the skin (13,38). In the studies on children population, side effects observed in different patients were limited to mild erythema, hyperpigmentation, itching, and mild peeling of the skin (14).

4.2.3 | Topical contact sensitization

Anthralin

Bullae, generalized pruritus, lymphadenopathy, and hyperpigmentation are the most common adverse effects of anthralin (39). In the

studies on children population, 4 patients stopped the use of anthralin due to skin irritation (17).

Clobetasol and Hydrocortisone

Few local side effects have been reported during the short-term (~3 weeks) application of topical clobetasol propionate despite its clinical potency. Transient burning, stinging, or tingling, pruritus, pyoderma/folliculitis, brittle skin and/or "cracking," telangiectasia, or striae are the common adverse effects of clobetasol. Some patients using clobetasol developed atrophy in the treated areas (40). In the studies on children population, limited herpes zoster was observed in one patient receiving systemic corticosteroids (33).

Methotrexate

The main short-term adverse effects are hematologic, particularly pancytopenia. Other adverse effects include mucositis, oral and/or gastrointestinal ulcers, photosensitivity, rash, acne, anorexia, alopecia, diarrhea, nausea, and interstitial pneumonitis, particularly in patients with hypoalbuminemia. Long-term adverse effects are mostly hepatic and may range from elevated transaminases to steatosis and cirrhosis. Other long-term effects include pulmonary fibrosis, malignancy (increased risk of lymphoma in patients with psoriasis or rheumatoid arthritis), and increased risk of occlusive vascular disease (33). In the studies on children population, nausea was reported in one patient on the day of MTX administration (15).

4.3 | Summary of evidence

Management and treatment of AA could vary by different dermatologists (41,42). Several treatments have been evaluated through randomized controlled trials to determine the most effective treatments for AA. On the other hand, the rate of hair loss and the patient's age are the most important factors in the treatment approach. Therefore, the selection of the best treatment options can be challenging facing physicians (43). Therapies used for AA include intralesional injection of corticosteroids, topical corticosteroids, topical minoxidil, topical immunotherapy, and laser therapy. However, treatment options for AA in children are more limited than in adults and there is no reliable treatment for them; whereas, children require more effective treatments without serious side effects (16,44). Based on the results of the present systematic review, the methods used in the 10 reviewed articles for the treatment of Alopecia Areata in children included topical use of SADBE, laser therapy, use of Anthralin, tofacitinib, Clobetasol, and methotrexate. The highest percentage of complete hair regrowth (79.6%) was related to the topical application of SADBE. However, for laser treatment, the rate of regrowth was reported to be above 50% (63.6%). In other topical methods (Anthralin, Clobetasol, and methotrexate), the complete response was below 50% (between 30 and 35%). However, in the methotrexate group, 77%–99% regrowth was reported in 30.76% of treated patients.

The results demonstrated that during the follow-up period (with an average of 3.96 years) in the topical immunotherapy group, 66.66% of studies (2 of 3 articles) reported a recurrence after treatment, and no reporting in one article. In one article, 44% of patients treated with SADBE had a recurrence, and in another article, 7 of 10 patients with complete hair regrowth experienced a recurrence within one month to 3 years after treatment, and in other 3 patients, mild recurrence was observed within 4 to 21 months after treatment. However, in the light-based therapy group with an average follow-up period of 6 months, there was no report of recurrence after treatment; it should be noted that this may be a short time for assessment of the recurrence after treatment. Also, in the group of patients treated using contact sensitizer with hair regrowth below 50%, recurrence was reported during the follow-up period (average 2.25 years). In one article, recurrence occurred in two patients during the treatment period and in one patient 4 months after the cessation of treatment, and in another article, the recurrence time was not reported. No serious side effects were reported in the treatment groups, and the observed side effects were all tolerable.

Dall'Oglio et al. reported that 80% of patients treated with SADBE recovered without any side effects, and no significant differences in age, sex, or duration of disease were observed in comparison with controls (5). While Rangu et al. stated that the prevalence of AA is higher in girls than boys. Their study was consistent with other studies on children with AA in the United States, Europe, India, and Kuwait (7). In a systematic study, the evaluation of effectiveness of the combination therapy (methotrexate plus corticosteroids) versus single therapy (methotrexate), and the relative effects of methotrexate in adults versus children, showed that methotrexate has an acceptable effect in patients with severe AA. A better rate of response to methotrexate treatment was observed in adults, comparing with pediatric patients. The results of combination therapy showed a higher rate of complete response compared to treatment with methotrexate alone. The majority of patients had recurrences due to reduced treatment. The rates of complications in adult patients and children were acceptable and similar (45). The results of another systematic review, which conducted to determine the effectiveness of topical diphenylcyclopropenone treatment for AA, showed that the mean response rate of DPCP treatment in 26 studies was 53.75% (46). In another review study on treatment with topical immunotherapy for patients with AA, 45 studies with a total of 2 227 patients were reviewed, and the results showed that the overall rate of hair regrowth in patients with AA was 65.5% (74.6% for patchy alopecia and 54.5% for alopecia totalis / universalis). However, the rate of complete regrowth was 32.3%. The recurrence rate in patients receiving maintenance treatment was 38.3% and in those who did not receive maintenance treatment was 49% (47).

Based on the results of the present systematic review, the mean response and recurrence in the immunotherapy group were 53.8% and 57%, respectively.

Evaluation of the effectiveness of systemic pulse corticosteroid treatment in a systematic review on 41 studies with 1 078 patients (213 of whom were children) showed that the complete response

rate was 43% in the study population other than the children, and 51% in the studies examined children. The recurrence rate was low in the whole study population (17%) but higher for the pediatric population (60%). Side effects, including epigastric pain, fatigue, headache, acneiform rash, and palpitations, were seen in 21% of the study population, but all of them were minor (48).

However, according to the present study, the highest recurrence rate was 57% (observed in the topical immunotherapy group).

Another study performed on 11 children with AA in the scalp showed that regrowth occurred in 60% of excimer laser-treated patches, after 12 weeks. The results of their study showed that the 308-nm Excimer laser system may be an effective and safe treatment for children with small patches of AA on the scalp. However, similar to other treatments used for AA, recurrence after discontinuation of treatment is still a major concern (14). The use of laser in combination with many local agents already available can be considered as a treatment option (13).

According to the present study, no recurrence was reported after treatment in the laser treatment group, maybe relating to the average follow-up period of 6 months, which seems not appropriate for evaluating the recurrence rate.

Comparison of different treatment groups demonstrated that the most effective therapeutic method was the use of topical immunotherapy (with an average effectiveness of 53.8%), followed by light/laser therapy (with an average effectiveness of 52.55%) and the use of contact sensitizer (with an average effectiveness of 30.86%). However, the rate of recurrence after treatment in the group of patients treated with contact dermatitis topical drugs (mean 43.53%) was lower than the topical immunotherapy group (mean 57%). No recurrence was reported in the laser therapy group. On the other hand, two methods of local immunotherapy and laser therapy were well tolerated by the children, and no serious side effects were observed in all three treatment groups.

Moreover, identifying effective factors in treatment and recovery, such as vitamin levels in the body, is an important issue (49). Although several treatments have been proposed and used for AA, there is still no optimal treatment protocol for this disease, and recurrence of the disease is usually observed. Based on the results of the present review, studies performed on topical immunotherapy have reported a high percentage of hair regrowth, and more than 50% efficacy in hair regrowth was reported in the group of patients treated with the light/laser therapy method; also, no serious side effects were observed in these treatment groups and both methods were well tolerated by children. Therefore, a combination of these two treatments, namely local immunotherapy and light/laser therapy, can be suggested for the treatment of this disease in children.

4.4 | Conclusion

Based on the results of the present review, studies performed on topical immunotherapy have reported a high percentage of hair regrowth (average about 54% and highest regrowth about 80%), and more than 50% efficacy in hair regrowth was reported in the group of patients treated with the light/laser therapy method (average about 52.5% and highest regrowth about 64%). Also, no serious side effects were observed in these treatment groups and both methods were well tolerated by children. Therefore, a combination of these two treatments, namely local immunotherapy and light/laser therapy, can be suggested for the treatment of this disease in children. It should be notified that between evaluated methods, immunotherapy, light/laser therapy, and contact dermatitis induced by Anthralin, although anthralin had the lowest hair regrowth rate, anthralin-related acceptable responses were the most durable and sustained ones that are of great importance for treatment selection for each individualized case.

4.5 | Limitations

Since the number of systematic review studies for this topic could be large, case report articles were not included in the present study.

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CONFLICT OF INTERESTS

All the authors declare that there is no conflict of interest.

AUTHOR'S CONTRIBUTION

Elham Behrangi, Masoumeh Roohaninasab, Afsaneh Sadeghzadeh-Bazargan, and Mohammadreza Ghassemi: Study concept and design. Mohammadreza Ghassemi, Farnoosh Seirafianpour, and AzadehGoodarzi: Data collection. Niloufar NajarNobari and Mohammadreza Ghassemi: Analysis and interpretation of data. Farnoosh Seirafianpour, Azadeh Goodarzi, Milad Dodangeh and Mohammadreza Ghassemi: Drafting of the manuscript. Elham Behrangi, Masoumeh Roohaninasab, and AzadehGoodarzi: Study supervision. All authors critical revision of the manuscript for important intellectual content and final approval of the version to be published.

ETHICAL STATEMENT

Authors declare human ethics approval was not needed for this study.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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