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Treatments for alopecia areata: A systematic review and network meta-analysis

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Abstract

Existing guidelines form no consensus for alopecia areata (AA) treatment due to the absence of a universal standard treatment and arbitrary selection of reference arms in randomized control trials (RCTs). The aim is to identify the best treatment and to rank treatments using systematic review and network meta-analysis. Data were extracted by the two investigators independently. Odds ratio (OR) of treatment success rate was pooled using the frequentist weighted least squares approach to random-model network meta-analysis. RCTs providing data of treatment success rate from PubMed, EMBASE, Web of Science, and manual search were included. About 54 RCTs consisting of 49 treatments and 3149 patients were included. Pentoxifylline plus topical corticosteroids had the highest treatment success rate compared with "no treatment," followed by pentoxifylline alone, topical calcipotriol plus narrowband ultraviolet radiation B phototherapy, topical calcipotriol, intralesional corticosteroids, systemic corticosteroids, minoxidil plus topical corticosteroids, topical bimatoprost, psoralen ultraviolet radiation A phototherapy, and tofacitinib. Even with the network meta-analysis, the best treatment because of independent loops and wide confidence intervals could not be identified. Treatment options above may be reasonable strategies, but further comparison is required.

KEYWORDS
alopecia areata, network meta-analysis, systematic review, treatment, treatment efficacy

1 | INTRODUCTION

Alopecia areata (AA) is a common autoimmune disease that targets hair follicles with a prevalence of approximately 0.1% and a lifetime incidence of approximately 1.7%.[1-5] AA is the third most prevalent nonscarring hair loss disease.[1,2] There is no gender difference in prevalence of AA, although AA is the most common autoimmune disease in men.[2,5] AA sometimes co-occurs in patients with atopic dermatitis, thyroid disease, lupus erythmatosis, and other autoimmune diseases.[3] The clinical pattern of AA presents with single to multiple patches with well-demarcated borders (localized AA), sometimes progressing to complete scalp hair loss (alopecia totalis, AT) or to total body hair loss (alopecia universalis, AU).[1,2,5] Alopecia ophiasis (AO) is an additional subtype that is often difficult to treat.[6] Although not life-threatening, AA can cause psychological effects on patients including anxiety and, occasionally, depression,[3-5] and thus is a serious clinical concern.

Genetic, environmental and immunological factors, including T lymphocytes and cytokines, play a crucial role in pathogenesis.[1,3,6,7] A peribulbar lymphocytic infiltrate is an expected histological feature of AA and is representative of activated T lymphocytes.[5] However, overall AA pathogenesis remains controversial, which results in nonspecific and unsatisfactory treatment strategies.[3,8] Although many treatment options such as topical/intralesional therapies, systemic therapies, and phototherapies are available, AA remains a clinical challenge because only 30% of patients experience long-lasting remissions.[1,3]

Many guidelines present a long list of AA treatment strategies[6,9,10]; ; however, no guideline can suggest the best treatment option for AA due to the absence of a universal standard treatment and arbitrary selection of reference arms in randomized control trials (RCTs). Although some head-to-head meta-analyses for AA treatment have been published, these studies were not designed to identify the best treatment among a great variety of treatment options. The aim of this study is to identify the best treatment for AA and rank currently available treatments using systematic review and network meta-analysis.

2 | METHODS

2.1 | Protocol registration

The protocol has been submitted to the website of International Prospective Register of Systematic Reviews on 20th August 2019.[11] This protocol complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[12]

2.2 | Study search

An electronic search was performed on August 10, 2019. The formula used for Pubmed can be found in the Supporting Information Method. Similar formulas were used for Web of Science and Embase. The two authors (T.F. and N.H.) performed additional manual searches independently. If any discrepancies were found during the study selection process, the authors discussed to resolve the discrepancy.

2.3 | Inclusion criteria

2.3.1 | Publication type and trial design

Randomized trials comparing two or more AA treatments were included, regardless of language. Non-full articles such as brief reports, letters, and conference abstracts were accepted. Selected articles provided data of treatment success rate by assessment of improvement of AA.

2.3.2 | Patients

Any AA such as localized AA, AT, AU, and AO was accepted, regardless of size and aggressiveness of the lesion and history of previous treatment. Studies focusing on patients with Androgenetic Alopecia (AGA) were excluded. Age, sex, and co-morbidities of patients were not questioned.

2.3.3 | Treatments

Our study included guideline-recommended treatment options.[6,9,10] The treatment option "no treatment" included both vehicle control and placebo. "Wait and see" was also regarded as "no treatment" because 80% of patients experience remission of AA without any treatment.[6,9] Corticosteroid treatments were subdivided into topical, intralesional, and systemic administration.

Any studies that compared two levels belonging to the same treatment were excluded. For example, a study comparing low-dose and high-dose NBUVB was excluded.

2.4 | Quality assessment

The quality of all original studies was assessed by using six domains of Cochrane Risk of Bias: selection, performance, detection, attrition, reporting, and other biases.[13]

2.5 | Outcomes

The primary outcome was odds ratio of treatment success rate. When data using two or more cutoffs for treatment success were available, we selected the data using the cutoff nearest to 50% improvement.

2.6 | Data extraction

Data were extracted by the two authors (T.F. and N.H.) independently. When any articles contained the results from two clearly independent trials, these two trials were treated separately. When only two arms of a three-arm study met inclusion criteria, only data from those two arms were included. Intention-to-treat analysis was preferred to full-analysis-set analysis and per-protocol analysis.

2.7 | Statistical analyses

Treatment success rate was compared using odds ratio, logarithm-converted, then pooled. The frequentist weighted least squares approach to random-model network meta-analysis was applied.[14-16] A league table for treatment effect differences and their 95% confidence intervals (95% CI) was presented. For a forest plot, "no treatment" and the therapy with the highest success rate was selected as the common reference comparator. For the network meta-analysis, the "netmeta" command in "netmeta" package of R was performed.[16] Fixed-model network meta-analysis was performed for sensitivity analysis when heterogeneity was observed.

3 | RESULTS

3.1 | Search results and characteristics of included studies

The PRISMA flowchart for the study search is shown in Figure 1. The search strategies yielded 1380 studies from the databases. Manual

searches found 10 additional studies. Of the 1380 studies found through the primary search, 355 and 786 were excluded because of article duplication and title/abstract screening, respectively, and 239 potentially eligible studies were identified (Figure 1). Full texts of all potentially eligible studies were assessed, and 185 were excluded for reasons shown (Figure 1). In all, 54 studies met inclusion criteria (Figure 1; Table 1).

The 54 RCTs included 49 treatment options and 3209 patients (Table 1), whose term of follow-up ranged 12 weeks to 1 year (Table 1). Detailed information about each trial is summarized in Table 1.

According to the Cochrane Risk of Bias evaluation, 46 studies had at least one domain of high risk of bias (Table S1).

3.2 | Six independent loops

In network meta-analysis, indirect comparison is only feasible when the concerned treatments are directly or indirectly linked with other trials. Treatment strategies linked with each other make a "loop." Included studies evaluated a great variety of treatments, which separately belonged to six independent loops (Figure 2). The majority of RCTs and treatments belonged to the largest loop. Contact immunotherapies constituted the second largest loop. The third largest loop included trials that evaluated Chinese herbal medicine. The other three loops included one two-arm trial each. For convenience, we named six loops as the main loop, the contact immunotherapy loop, the Chinese herbal medicine loop, the Janus kinase inhibitor

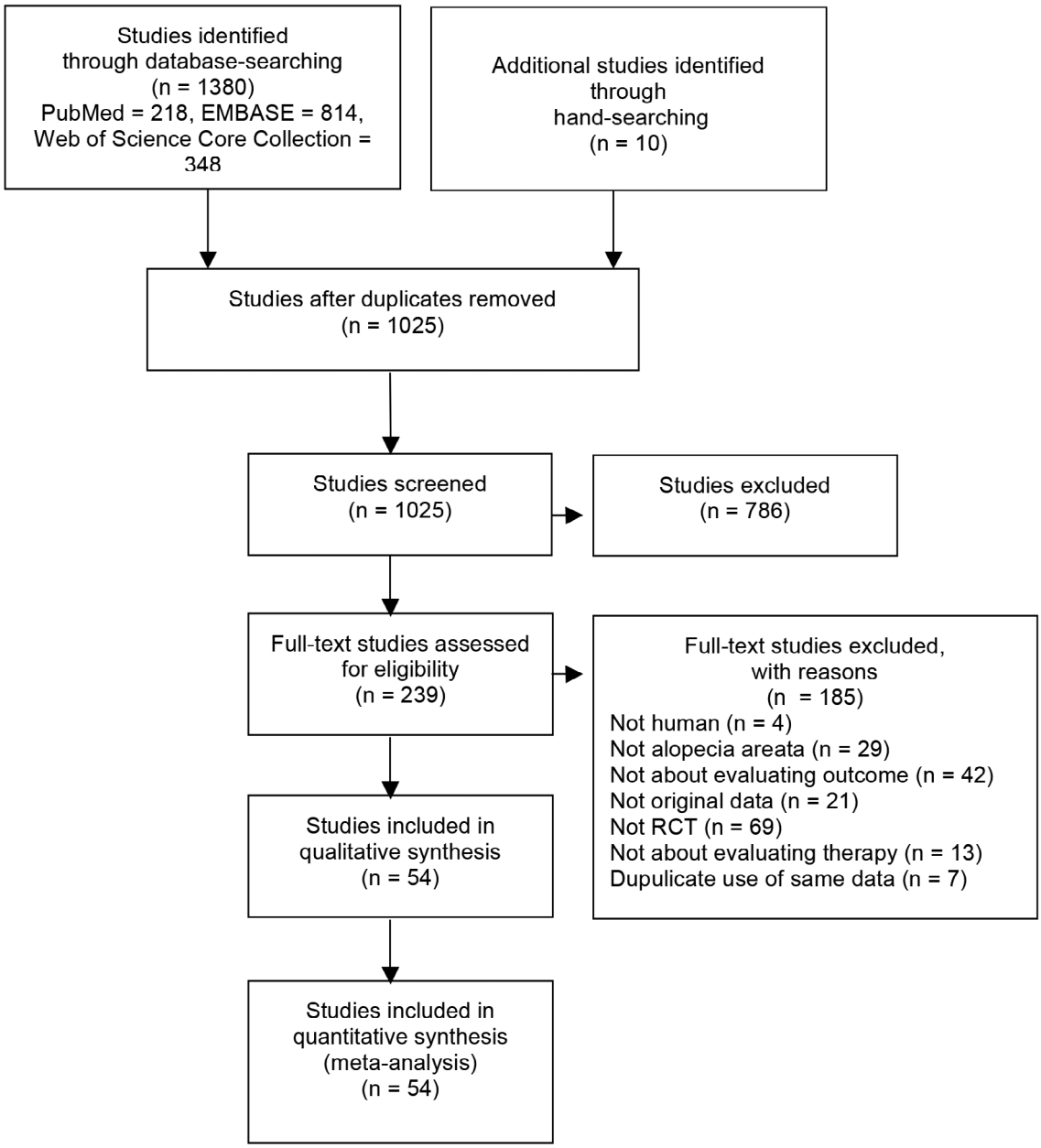

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses flow chart for study search

TABLE 1 Characteristics of included studies

Author	Year	Country	Type	Severity	Site	Unit	N	Follow up	Treatment 1	Treatment 2	Treatment 3, 4, 5
Almutairi	2019	Kuwait	p/t/u	Severe	NA	pe	80	6 m	Ruxolitinib (20 mg)	Tofacitinib (5 mg)	
Aman	2010	Pakistan	p	<3 patches	scalp/beard	pe	50	3 m	5% topical minoxidil	Topical 5% minoxidil solution + betamethasone dipropionate cream (0.05%)	
Bokhari	2018	Australia	u	NA	NA	di	64	12w	Tofacitinib ointment (2%)	Ruxolitinib ointment (1%)	Tx 3: clobetasol dipropionate ointment (0.005%) Tx 4: no treatment
Borchert	2016	The United States	NA	Eyelash Assessment score <3	Eyelash	pe	15	4 m	Bimatoprost solution (0.03%)	No treatment	
Charuwichitratana[a]	2000	Thailand	p	Mean affected area (9.52 cm2)	NA	pe	70	12w	Desoximetasone cream (0.25%)	No treatment	
de-Prost[a]	1986	France	p/t/u	Severe	NA	pe	43	6 m	Cyclosporin lotion (100 mg/mL)	No treatment	
Devi	2015	Pakistan	p	<3 patches	NA	pe	226	12w	Intralesional triamcinolone acetonide (10 mg/mL)	Betamethasone valearate cream (0.1%)	
El-Ashmawy	2018	Egypt	p	<25% of scalp	Scalp/beard	pe	100	20w	Latanoprost 0.1% lotion	5% topical minoxidil	Tx3: Betamethasone valerate 0.1% solutionTx4: latanoprost lotion + betamethasone valerate solutionTx5: no treatment
El-Mofty	2019	Egypt	p	Mean SALT (37)	scalp	pe	40	3 m	PUVA (topical psoralen)	Intralesional injection of triamcinolone acetonide (5 mg/mL)	
El-Taieb	2017	Egypt	p/t/u/o	NA	Scalp	pe	90	3 m	5% topical minoxidil	PRP	No treatment
El-Taweel	2019	Egypt	NA	<50% of scalp	NA	pe	75	NA	Intralesional injection of triamcinolone acetonide	Intralesional injection of triamcinolone acetonide + pentoxifylline	Intralesional injection of pentoxifylline
Fenton[a]	1983	The United Kingdom	p/t/u/o	NA	NA	pe	30	3 m	1% topical minoxidil	No treatment	
Fransway	1988	The United States	p/t/u	>65% of scalp	Scalp	di	52	12 m	3% topical minoxidil	No treatment	
Georgala	2006	Greece	p/t/o	NA	Scalp	pe	32	12w	Inosiplex (50 mg/kg)	No treatment	

TABLE 1 (Continued)

Author	Year	Country	Type	Severity	Site	Unit	N	Follow up	Treatment 1	Treatment 2	Treatment 3, 4, 5
Gupta	2019	India	p/t/o	Moderate to severe	Scalp	pe	50	4 m	Azathioprine pulse (300 mg)	Betamethasone (5 mg)	
Guttman-Yassky	2018	The United States	p/u	Extensive	NA	pe	11	24w	Secukinumab (300 mg)	No treatment	
Hay	1998	Scotland	NA	NA	NA	pe	84	7 m	Essential oils	No treatment	
Hossain	2015	Bangladesh	p	Not extensive	Scalp/elsewhere	pe	60	12w	Topical tacrolimus (0.1%)	Topical clobetasol propionate (0.05%)	
Jaiswal	2018	India	p/o	Mean SALT (11.7)	Scalp/face	pe	60	12w	Calcipotriol ointment (0.005%)	Calcipotriol ointment (0.005%) + NB-UVB	No treatment
Jalali	2014	Iran	p	1–4 of lesions	Scalp	pe	80	3 m	Elidel cream (1%)	Elidel cream (1%) + tretinoin (0.05%)	
Kar	2005	India	p	Severe	Scalp/body	pe	43	3 m	Prednisolone (200 mg)	No treatment	
Khoury	1992	The United States	NA	Scalp hair loss (26%-99%)	Scalp	pe	20	12w	5% topical minoxidil	No treatment	
Kuldeep	2011	India	p/t/u/o	Not extensive	Scalp/beard/eyebrow	pe	78	12w	Betamethasone valeratetopical foam (0.1%)	Intralesional triamcinolone acetonide (10 mg/mL)	Tacrolimus ointment (0.1%)
Lai	2019	Australia	p/t/u	Moderate to severe	NA	pe	36	3 m	Cyclosporine (4 mg/kg)	No treatment	
Mehta[a]	2011	India	NA	NA	NA	pe	51	3 m	Liquid phenol (20%)	Liquid phenol (20%) + 2% topical minoxidil	Liquid phenol (20%) + betamethasone (1 mg)
Mikhaylov	2019	The United States	NA	Moderate to severe	Scalp	pe	30	24w	Apremilast (30 mg)	No treatment	
Perini	1994	Italy	p/u	NA	NA	pe	13	6 m	Imipramine (75 mg)	No treatment	
Pipoli	1995	Italy	p/t	Severe	Scalp/eyebrow/eyelash	pe	30	6 m	SADBE	Interferon alpha	SADBE + interferon alpha
Price	2008	The United States	p/t/o	Moderate to severe	NA	pe	62	12w	Subcutaneous efalizumab (1 mg/kg)	No treatment	
Price_1987A	1987	The United States	p/t/u	>50% of scalp	Scalp	pe	30	1y	3% topical minoxidil	No treatment	
Price_1987B	1987	The United States	NA	25%-100% of scalp	Scalp	pe	30	12w	3% topical minoxidil	No treatment	
Rinaldi	2019	Italy	p	NA	NA	pe	60	90d	TR-M-PRP plus comprising biomimetic peptides mimicking PRP	No treatment	
Rongioletti	1992	Italy	p/t/u	Severe	NA	pe	85	6 m	10% cyclosporin gel (olive oil 10%. ethanol 10%, other vehicles 70%)	No treatment	

(Continues)

TABLE 1 (Continued)

Author	Year	Country	Type	Severity	Site	Unit	N	Follow up	Treatment 1	Treatment 2	Treatment 3, 4, 5
Ross[a]	2005	Canada	NA	Severe	Eyebrow	di	22	16w	Topical latanoprost (3 μg)	No treatment	
Sardesai	2012	India	p	<25% of scalp	Scalp	pe	30	3 m	Triamcinolone acetoniden (10 mg/mL)	Betamethasone dipropionate losion (0.005%)	Tx3: 5% topical minoxidilTx4: anthralin (1.15%) + salicylic acid (1.15%) ointmentTx5: no treatment
Sasmaz	2005	Turkey	p	1< affected area <30	NA	pe	31	12w	20% azelaic acid	0.5% anthralin	
Shapiro	1993	Canada	NA	Severe	Scalp	di	13	24w	DPCP	DPCP + 5% topical minoxidil	
Strober	2009	The United States	p	Severe	Scalp	pe	45	12w	Alefacept (15 mg)	No treatment	
Swanson	1981	The United States	p/t/u	Severe	NA	pe	22	6 m	DNCB	No treatment	
Talpur	2009	The United States	p/t/u	>2 distinct patches	Scalp	di	84	24w	1% bexarotene gel	No treatment	
Thuangtong[a]	2012	Thailand	t/u	Recalcitrant	Scalp	di	40	4 m	Botulinum toxin A injection (50 units/2.5 mL)	No treatment	
Tiwary	2016	India	p/o	>20% of scalp	Scalp	pe	24	6 m	SADBE	DPCP	
Tosti	2006	Italy	NA	Moderate to severe	NA	di	68	12w	New topical formulation of clobetasol propionate (0.05%)	No treatment	
Tosti	1991	Italy	t/u	NA	NA	pe	26	9 m	Topical 10% cyclosporine solution	PUVA	Intravenous thymopentin (50 mg)
Trink[a]	2013	Italy	p	NA	NA	pe	45	1y	Intralesional injection of PRP	Intralesional injection of triamcinolone acetonide (2.5 mg/mL)	No treatment
Ustuner	2017	Turkey	p	1–6 of patches	Scalp/beard	pat	231	6 m	Injection of triamcinolone acetonide or betamethasone dipropionate	No treatment	
Vestey[a]	1986	Scotland	p/t/u/o	Severe	NA	pe	50	16w	1% topical minoxidil	No treatment	
Warin[a]	1979	The United Kingdom	p/t	Extensive	NA	di	30	40w	DNCB	No treatment	
White[a]	1985	England	NA	NA	NA	pe	15	16w	3% topical minoxidil	No treatment	

TABLE 1 (Continued)

Author	Year	Country	Type	Severity	Site	Unit	N	Follow up	Treatment 1	Treatment 2	Treatment 3, 4, 5
Xue[a]	2018	NA	NA	NA	NA	pe	150	3 m	Compound glycyrrhizin tablets	LingDan tablets	
Yang	2013	China	NA	Severe	Scalp/beard/body	pe	117	12 m	TGPC (900 mg) + CGT (75 mg)	CGT (75 mg)	
Yang	2012	China	NA	Mild and moderate	NA	pe	86	3 m	TGPC (1800 mg)	CGT (150 mg)	
Zaher	2015	Egypt	p	Mean SALT (7.6)	Scalp	pat	60	3 m	Mometasone furoate cream (0.1%)	Bimatoprost solution (0.03%)	
Zaib	2017	Pakistan	p	NA	NA	pe	80	3 m	5% topical minoxidil	No treatment	

[a]Means articles except for a full article.

Abbreviations: CGT, compound glycyrrhizin tablets (CGT); di, unit of divided area in a person; DPCP, diphenylcyclopropenone; DNCB, dinitrochlorobenzene; N, number of object; NA, not applicable; NB-UVB, narrow-band ultraviolet B therapy; o, type of ophiasis; p, type of patchy; pat, unit of patch; pe, unit of person; PRP, platelet-rich plasma; PUVA, psoralen-ultraviolet A therapy; SALT, severity of Alopecia Tool; SADBE, essential oils (thyme, rosemary, lavender, and cedar wood oils in a mixture of carrier oils), squaric acid dibutylester; t, type of totalis; TGPC, total glucosides of paeony capsule; u, type of universalis.

loop, the pimecrolimus loop, and the azelaic acid and anthralin loop (Figure 2).

3.3 | The main loop

The network plot of the largest main loop included 45 RCTs and 34 treatments (Figure 2). Topical and intralesional corticosteroids were also often used as reference arms.

In the random-model network meta-analysis of this main loop (I^2 = 57%, *P* for heterogeneity <.001, Figure 3), PTX plus topical corticosteroids had the highest treatment success rate (OR compared with "no treatment" 135.6, 95% confidence interval [95%CI] 11.3-1632.9, *P* < .001). Some other treatments had significantly higher success rates compared to "no treatment," but these success rates were not significantly lower than the best treatment, PTX plus topical corticosteroids (Figure 3). In other words, these treatments are potentially best: PTX alone (OR compared to "no treatment" 86.5, 95%CI 7.5-993.3, *P* < .001), topical calcipotriol plus NBUVB (OR 58.8, 95%CI 3.6-954.9, *P* = .004), topical calcipotriol (OR 40.5, 95%CI 2.5-655.9, *P* = .009), intralesional corticosteroids (OR 21.0, 95%CI 6.5-67.8, *P* < .001), systemic corticosteroids (OR 16.9, 95%CI 3.0-95.3, *P* = .001), minoxidil plus topical corticosteroids (OR 15.83, 95%CI 1.2-204.7, *P* = .034), topical bimatoprost (OR 11.8, 95%CI 1.7-84.0, *P* = .014), PUVA (OR 10.88, 95%CI 1.1-105.6, *P* = .040), and tofacitinib (OR 6.93, 95%CI 1.1-44.7, *P* = .042).

Corticosteroids did not show significantly different success rates through three administration routes, that is, intralesional, topical, and systemic corticosteroids.

About 19 treatments out of 34 in the main loop did not show significantly higher success rates compared to "no treatment" (Figure 3).

Results from a fixed-model network meta-analysis of the main loop as a sensitivity analysis was compatible with that from the random-model analysis (Figure S1).

3.4 | The contact immunotherapy loop

The second largest loop consisted of three trials and mainly evaluated contact immunotherapies such as DPCP and SBDBE (Figure 2). Network meta-analysis of this loop did not find heterogeneity (I^2 = 0%, *P* for heterogeneity = 1, Figure 4).

Patients treated with SADBE plus IFNA showed the highest treatment success. OR of treatment success for SADBE plus IFN compared to DPCP was 16.0 (95%CI 1.5-170.4, *P* = .022). SADBE plus IFNA showed greater treatment success than DPCP plus topical minoxidil (OR 24, 95%CI 0.91-633.85, *P* = .057).

Again, no evidence was available to compare these immuno-contact therapies to treatment options in the main loop such as "no treatment," corticosteroid therapies, or PTX regimens.

3.5 | The Chinese herbal medicine loop

Some Chinese herbal medicines such as glycyrrhizin, LingDan, TGPC belonged to the third largest loop, Chinese herbal medicine (Figure 2).

The random-model meta-analysis with three trials evaluating four treatments revealed that TCPC.sys plus CGT had the highest success rate (I^2 = 0, P = 1). Compared to TCPC.sys plus CGT, CGT.sys alone (OR 0.3, 95%CI 0.1-0.6, P = .002), systemic LingDan (OR 0.1, 95%CI 0.0-0.3, P < .001), and systemic TGPC alone (OR 0.2, 95%CI 0.1-0.8, P = .020) led to lower success rates (Figure 4).

3.6 | The other three loops

The other three loops included one two-arm trial each (Figure 2). Therefore, meta-analysis was not required.

4 | DISCUSSION

Although some well-known guidelines list many therapeutic options for AA,[6,9,10] these guidelines do not specify the overall best treatment option. To our best knowledge, there are only three systematic reviews that compare multiple treatments of AA; however, they did not conduct network meta-analyses to rank all the treatment options comprehensively.[17-19] We have attempted to identify the best therapeutic option for AA using systematic review and network meta-analysis.

In the main loop, PTX plus topical corticosteroids had the greatest treatment success rate; however, some other treatments may be valid therapeutic options because they showed no significant difference in the treatment success rate when compared to PTX plus topical corticosteroids. In short, PTX alone, topical calcipotriol plus NBUVB, topical calcipotriol, intralesional corticosteroids, systemic corticosteroids, minoxidil plus topical corticosteroids, topical bimatoprost, PUVA, and tofacitinib currently have the greatest treatment success rates. We cannot recommend 19 treatments in the main loop that did not show significantly higher success rates compared with "no treatment" (Figure 3).

SADBE alone and SADBE plus IFNA in the contact immunotherapy loop and TGPC.sys + CGT.sys in the Chinese herbal medicine loop, which many dermatologists believe to be acceptable treatment for AA,[6,9,10] are also the best performing treatments in their respective loops. Future trials comparing treatments between loops are necessary to determine a universal best treatment for AA.

Although PTX plus topical corticosteroids and PTX alone showed the highest treatment success rates (Figure 3), the RCT evaluating these treatments was performed by ElTaweel et al (Table 1). PTX is a methylxanthine derivative, which inhibits phosphodiesterase and regulates cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), leading to anti-inflammatory effects by inhibiting pro-inflammatory cytokines.[20] PTX also regulates the activation of T lymphocytes and increases T-helper type 2 (Th2).[20] These functions of PTX might be beneficial for AA treatment. Future RCTs are needed to confirm this finding.

Calcipotriol plus NBUVB and topical calcipotriol showed the next best efficacy (Figure 3) in a study by Jaiswal et al (Table 1). It is known that NBUVB has a positive effect on vitamin D synthesis.[1] Vitamin D is important in regulation of the hair cycle, and calcipotriol is a vitamin D analog.[1] The immune mechanisms of calcipotriol in AA patients may involve B cells and T cells, which may inhibit autoantibody production from B cells and shift T cell response toward Th2.[1,21] The role of NBUVB in AA patients is not clear, but it has been described that NBUVB can penetrate and work in the deep dermis where the pathology of AA may take place and that NBUVB can induct T-cell apoptosis and down-regulate the immune attack against the hair follicle.[1,21] Future RCTs are required for confirmation.

Although the treatment success rate of corticosteroids is modest, they were included in many evaluated RCTs, which makes the data credible and establishes corticosteroids as one of the first line options (Figure 3, Table 1). Pulse therapy using high-dose corticosteroids for treatments of AA was first introduced in 1975.[22,23] Systemic corticosteroids, including high-dose oral pulse therapy, did not show greater efficacy when compared to intralesional injection or topical use of corticosteroids. Physicians may select intralesional injection or topical use when using corticosteroids based on differential side effects and costs.

Topical minoxidil was evaluated in many RCTs, but its treatment effect was lower than topical corticosteroids. The effect of minoxidil for the treatment of AGA has been confirmed by systemic reviews.[24,25] Minoxidil plus topical corticosteroids is effective but not superior to topical corticosteroids alone.

Among contact immunotherapies, DNCB was assessed in the main loop and did not perform better than other treatments. SADBE and DPCP are widely used immunotherapies and are evaluated in the contact immunotherapy loop (Figure 2). SADBE performs better than DPCP, and SADBE plus IFN is a potential efficacious combination.[26,27] Pipoli et al described the possible synergistic mechanism of SADBE plus IFN.[28] Namely, hyperemia caused by SADBE increases the absorption rate of IFN alpha at the intralesional level, enhancing local bioavailability of IFN alpha. The comparison of SADBE and DPCP to corticosteroids or even no treatment remains unknown.

TCPC plus CGT had the greatest treatment success rate among Chinese medicines for the treatment of AA. Future RCTs comparing Chinese medicines with other treatments is needed. Moreover, Chinese medicines are mainly used in East Asia and should be evaluated in other populations to confirm their effectiveness.

Some treatments recommended in previous reports or guidelines did not show significant efficacy (Figure 3). Immunosuppressants, such as azathioprine, cyclosporine, or tacrolimus, should not be selected without extenuating circumstances because they had lower treatment success rates than therapies mentioned above (Figure 3). Similarly, JAK inhibitors may have deleterious side effects without significant efficacy for treatment of AA. Some challenging treatment options, such as intradermal injection of botulinum toxin A, platelet-rich plasma (PRP), PUVA (topical psoralen), and secukinumab, also did not

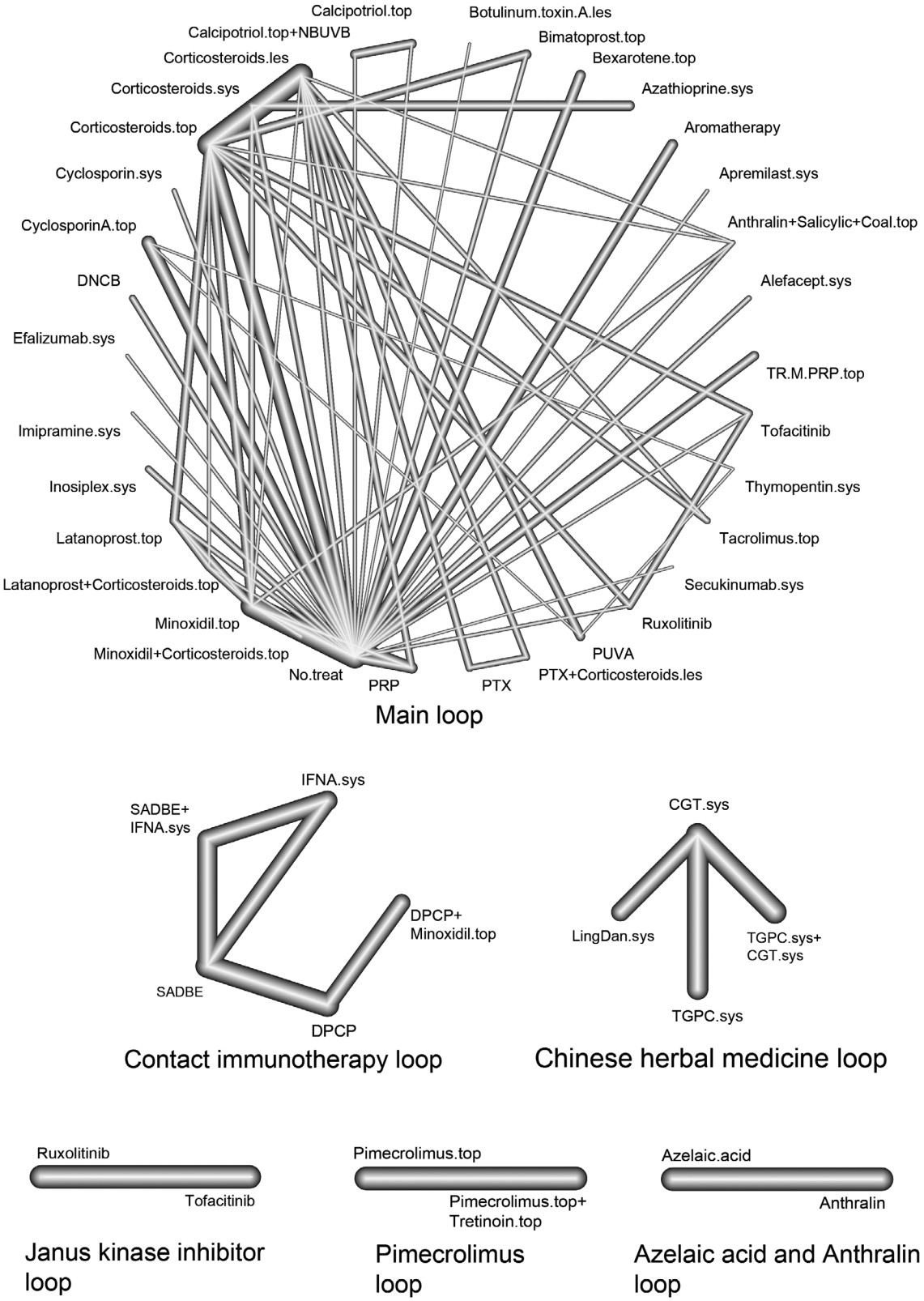

FIGURE 2 Network diagrams for the outcome of treatment efficacy in the meta-analyses of six independent loops. Abbreviations: topical use (.top), systemic use (.sys), intralesional injection (.les), no treatment (No. treat), compound glycyrrhizin tablets (CGT), diphenylcyclopropenone (DPCP), dinitrochlorobenzene (DNCB), interferon alpha (IFNA), platelet-rich plasma (PRP), pentoxifylline (PTX), psoralen-ultraviolet A therapy (PUVA), squaric acid dibutylester (SADBE), total glucosides of paeony capsule (TGPC), TR-M-PRP plus comprising biomimetic peptides mimicking PRP (TR.M.PRP.top)

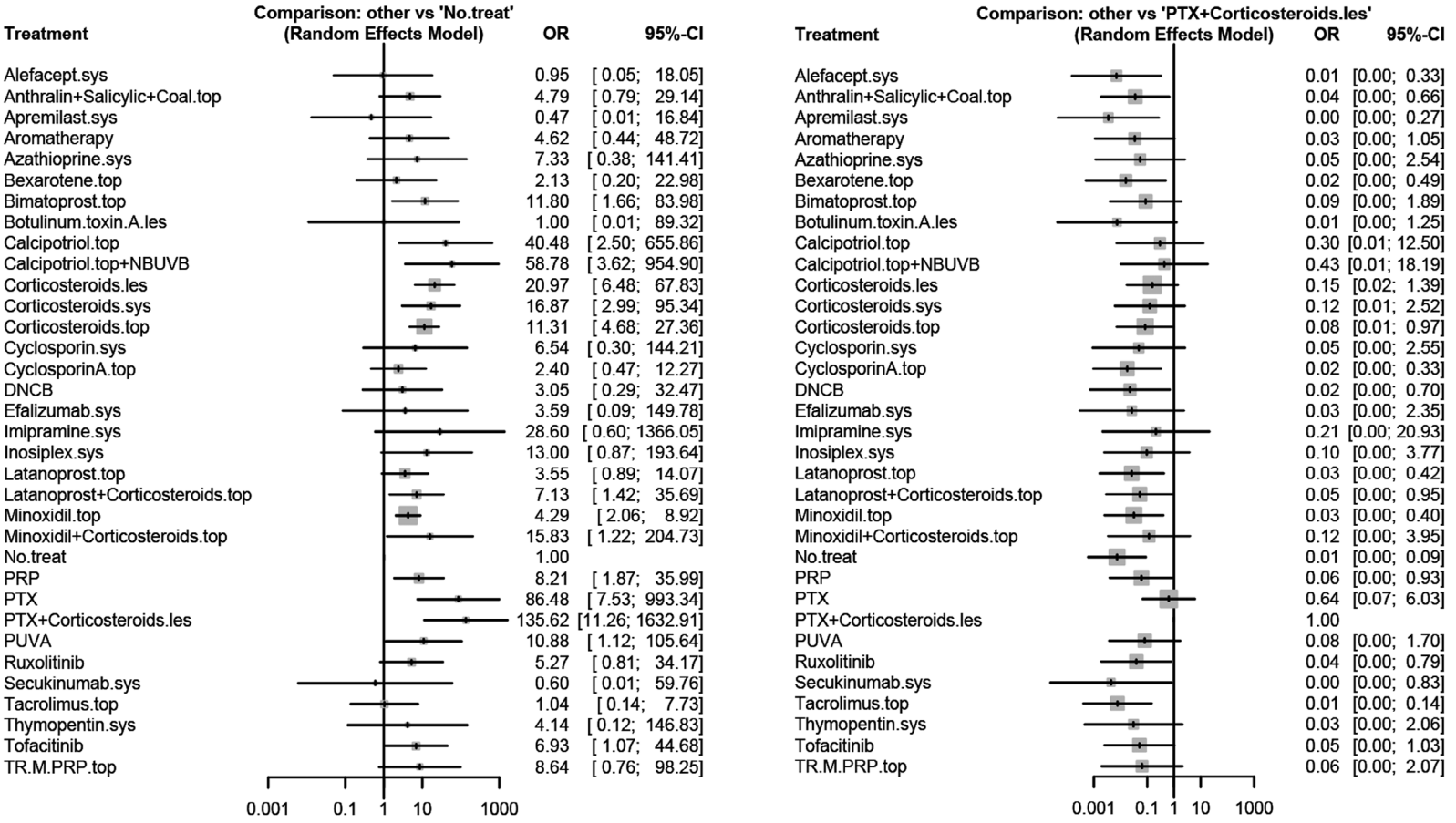

FIGURE 3 Forest plots for the outcome of treatment efficacy in meta-analysis of the main loop using random model compared to no treatment and compared to pentoxifylline plus topical corticosteroids. Abbreviations: topical use (.top), systemic use (.sys), intralesional injection (.les), no treatment (No. treat), compound glycyrrhizin tablets (CGT), diphenylcyclopropenone (DPCP), dinitrochlorobenzene (DNCB), interferon alpha (IFNA), platelet-rich plasma (PRP), pentoxifylline (PTX), psoralen-ultraviolet A therapy (PUVA), squaric acid dibutylester (SADBE), total glucosides of paeony capsule (TGPC), TR-M-PRP plus comprising biomimetic peptides mimicking PRP (TR.M.PRP.top)

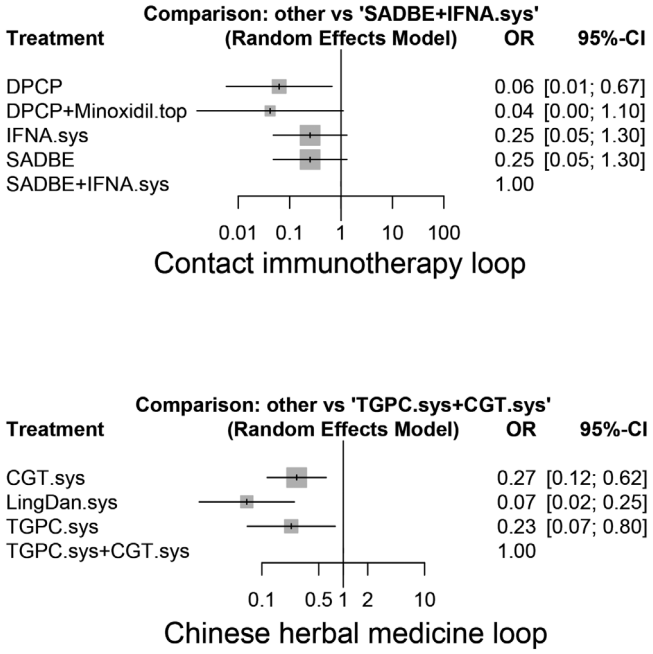

FIGURE 4 Forest plots for the outcome of treatment efficacy in meta-analyses of the contact immunotherapy loop and the Chinese herbal medicine loop. Abbreviations: topical use (.top), systemic use (.sys), compound glycyrrhizin tablets (CGT), diphenylcyclopropenone (DPCP), interferon alpha (IFNA), squaric acid dibutylester (SADBE), total glucosides of paeony capsule (TGPC)

show efficacy.[29-32] If physicians and patients wish to use these drugs, they should first consider other treatment options with higher treatment success rates.

One limitation of our study is the impossibility of comparing treatments in different loops. Second, regarding high-dose corticosteroid pulse therapy, to our best knowledge, there is one RCT assessing oral pulse prednisolone therapy, but no RCT was performed comparing intravenous high-dose pulses of methylprednisolone with other treatments.[6,33] The last is that we did not include RCTs published after 20th August 2019 because this protocol has been submitted to the website of International Prospective Register of Systematic Reviews on 20th August 2019.

5 | CONCLUSION

Gupta et al performed the systematic review and network meta-analysis regarding monotherapies for AA, revealing the significance of the treatment of intralesional and topical corticosteroids for mild AA and DPCP, laser, SADBE, topical minoxidil, and topical corticosteroids for moderate to severe AA.[34] We included six more RCTs that were published after Gupta et al had finished their search. Importantly, we included both monotherapies and combined therapies, whereas Gupta et al selected monotherapies.[34] However, our study as well as the study of Gupta et al revealed the significant treatment efficacy of intralesional and topical corticosteroids and topical minoxidil compared to no treatment for AA (Figure 3). SADBE performed better than DPCP based on our study (Figure 4).

This systematic review and network meta-analysis, which included 54 RCTs consisting of 49 treatment options and 3149 patients, suggested that pentoxifylline plus topical corticosteroids had the highest treatment success rate compared to "no treatment," although the superiority to many other treatments is uncertain. Even with the network meta-analysis, which enables indirect comparison, we could not identify the single best treatment for AA because of independent loops and wide confidence intervals. Further head-to-head comparison among reasonable treatments options is required.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Takeshi Fukumoto and Nobuyuki Horita performed the search. Takeshi Fukumoto, Rie Fukumoto, Masahiro Oka, Chikako Nishigori and Nobuyuki Horita analyzed the data. Takeshi Fukumoto, Masahiro Oka, Chikako Nishigori and Nobuyuki Horita designed the experiments. Takeshi Fukumoto, Rie Fukumoto, Elizabeth Magno, Masahiro Oka, Chikako Nishigori and Nobuyuki Horita wrote the manuscript.

DATA AVAILABILITY STATEMENT

All data are available in the main text or the supplementary materials.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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