Original Article | Annals of Dermatology 2023;35(3):190-204 • https://doi.org/10.5021/ad.22.168

Guidelines for the Management of Patients with Alopecia Areata in Korea: Part I Topical and Device-based Treatment

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Received September 13, 2022
Revised December 17, 2022
Accepted January 24, 2023

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Background: Alopecia areata (AA) is a chronic disease with an unpredictable disease course and severe psychological impact.
Objective: To provide evidence- and consensus-based insights regarding the treatment of patients with AA in Korea.
Methods: We searched for relevant studies on the topical and device-based treatment of AA in the literature from inception until May 2021. Evidence-based recommendations were also prepared. The evidence for each statement was graded and classified according to the strength of the recommendations. Hair experts from the Korean Hair Research Society (KHRS) voted on the statements, and an agreement of 75% or greater was considered as consensus.
Results: Currently, there remains a scarcity of topical treatments, which is supported by robust evidence from a number of high-quality randomized controlled trials. Current evidence supports the efficacy of topical corticosteroids, corticosteroid intralesional injection, and contact immunotherapy in AA patients. Topical corticosteroids and contact immunotherapy are recommended for pediatric AA. A consensus was achieved in 6 out of 14 (42.8%), and 1 out of 5 (20.0%) statements pertaining to topical and device-based treatments in AA, respectively. The expert consensus was from a single country, and the study may not cover all the treatments used.
Conclusion: The present study provides up-to-date, evidence-based treatment guidelines for AA based on the consensus reached among experts after considering regional healthcare circumstances, adding diversity to the previous guidelines.

Keywords: Alopecia areata, Device, Guideline, Korea, Therapeutics, Topical

INTRODUCTION

Alopecia areata (AA) is an autoimmune disease that causes varying degrees of hair loss. Clinicians must consider the significant impact of AA when making treatment decisions[1]. Currently, there is a lack of data evaluating the use of existing treatments. Additionally, the overall utility and preference of existing modalities vary widely among dermatologists[2].

In 2011, the Korean Hair Research Society (KHRS) released an informal version of treatment guidelines and several therapeutic guidelines for AA treatment have been published previously by professional working groups in various countries[2-9]. However, update clinical evidence and various attributes of a specific country can also affect the treatment decisions.

Thus, the KHRS intends to provide evidence-based consensus guidelines, which will help clinicians develop a management strategy for patients with AA.

MATERIALS AND METHODS

In April 2021, the KHRS appointed 12 working dermatologists with expertise in treating AA and formed a task force to develop guidelines. Key questions about the treatment for AA were then formulated, and evidence was gathered. When possible, treatment questions were posed with respect to the age and severity of AA. Severe AA was defined based on the Severity of Alopecia Tool score (SALT) ≥50.

Search strategy

A systematic literature search was conducted by the 12 panel members individually. Documents registered in PubMed, Korean Med, Cochrane library, and Scopus databases were searched from inception to May 30, 2021, using a combination of search terms, "alopecia areata," "child," "pediatric," "topical," "corticosteroid," "intralesional injection," "triamcinolone," "calcipotriol," "pimecrolimus," "tacrolimus," "minoxidil," "prostaglandin," "immunotherapy," "diphenylcyclopropenone," "diphencyprone," "DPCP," "squaric acid dibutylester," "SADBE," "anthralin," "eximer laser," "lamp," "phototherapy," "cryotherapy," "microneedle," "platelet rich plasma," "stem cell," "fractional laser," "Er:Glass laser," "non-ablative fractional laser," "low level laser therapy," "low level light therapy," "diode laser," "wig," "hair piece," and "quality of life." This systematic literature review was registered with PROSPERO (CRD42021250392) and was exempted from approval by the institutional review board (07-2021-30).

Study selection

The members primarily excluded irrelevant data from the search results by assessing the titles and abstracts and evaluated the level of recommendation (LOR) and grade of recommendation (GOR) by examining the original text.

Evaluation of the literature and consensus process

The members primarily evaluated the evidence for each statement, and the strength of the recommendation was classified according to the criteria in Table 1[10]. Consequently, a total of 51 out of 60 board members of the KHRS participated in three discrete rounds of online voting between September and December, 2021. Participants voted by scoring number between 1 and 9 for the degree of agreement (1 to 3 indicating disagreement, 4 to 6 indicating neutrality, and 7 to 9 indicating agreement). A consensus was defined as more than 75% of all participants scoring between 7 and 9.

RESULTS

Topical treatment

A total of 14 statements for various topical treatments for AA were developed (Table 2), and a consensus was reached in six out of 14 statements (42.8%).

Table 1. LOR and strength of the recommendations

Strength of recommendation		LOR	
A	Consistent level 1 studies	1a	Meta-analysis or systematic review of RCTs
		1b	Individual RCTs
B	Consistent level 2 or 3 studies or extrapolations* from level 1 studies	2a	Systematic review of cohort studies
		2b	Individual cohort study (including low- quality RCT)
		3a	Systematic review of case-control studies
		3b	Individual case-control study
C	Level 4 studies or extrapolations from level 2 or 3 studies	4	Case series (and poor-quality cohort and case-control studies)
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level	5	Expert opinion

LOR: level of recommendation, RCT: randomized controlled trial. *Extrapolations are where the data are used in a situation that has potentially clinically important differences from the original study situation.

Table 2. Evidence-based statement and expert consensus of topical treatment

Statement	Level of evidence	Strength of recommendation	Percentage of participants with score ≥7	Average agreement score (range)	Consensus
We recommend topical or intralesional corticosteroid therapy alone or in combination for adult patients with AA.	2b	B	100.0	8.8	Yes
We recommend topical corticosteroid for pediatric patients with AA.	2b	B	98.0	8.5	Yes
We conditionally recommend intralesional corticosteroid for pediatric patients with AA.	4	C	24.5	5.5	
We recommend high potency topical corticosteroid over low potency topical corticosteroid for pediatric patients with AA.	1b	B	73.5	7.2	
We conditionally recommend topical calcineurin inhibitor for adult patients with AA.	2b	C	26.5	5.6	
We conditionally recommend topical calcineurin inhibitor for pediatric patients with AA.	4	C	24.5	5.6	
We conditionally recommend topical calcipotriol for adult patients with AA.	2b	C	16.3	4.9	
We conditionally recommend topical minoxidil for adult patients with AA.	2b	C	81.6	7.2	Yes
We conditionally recommend topical minoxidil for pediatric patients with AA.	4	C	81.6	7.0	Yes
We conditionally recommend topical prostaglandin analogs for patients with AA of eyelashes.	2b	C	65.3	6.7	
We recommend contact immunotherapy for adult patients with AA.	2a	B	73.5	7.2	
We recommend contact immunotherapy using diphenylcyclopropenone for adult patients with severe AA.	2b	B	91.8	8.2	Yes
We recommend contact immunotherapy for pediatric patients with AA.	2b	B	79.6	7.3	Yes
We conditionally recommend topical anthralin for patients with refractory AA.	4	C	18.4	4.8	

AA: alopecia areata.

1) Topical corticosteroid or intralesional corticosteroid for adult AA patients

We recommend the use of topical or intralesional corticosteroid therapy alone or combination for patients with AA (LOR: 2b, GOR: B, agreement rate [AR]: 100%).

There are three randomized controlled trials (RCTs) in adult AA patients[11-13]. In all three studies, intralesional injection was performed with triamcinolone acetonide (TA) 10 mg/ml (0.1 ml/cm^2) at 3-week intervals for 12 weeks. Two out of three studies reported that the efficacy of intralesional injection was superior to that of topical corticosteroid[11,12]. In contrast, Suchonwanit et al.[13] divided 148 adult AA patients into three groups: 1) topical corticosteroid, 2) intralesional injection, and 3) combination of topical corticosteroid and intralesional injection, and all three groups showed significant hair growth without significant differences between groups.

A systematic review and meta-analysis[14] evaluated the optimal protocol for TA-intralesional injection[11,12,15-18]. The concentration of TA ranged from 2.5 mg/ml to 10 mg/ml, and intralesional injection was repeated every 3 to 4 weeks and for up to 6 months. Skin atrophy occurred in 4/120 patients (3.3%) treated with 5 mg/ml and 12/59 (20.3%) treated with 10 mg/ml of intralesional injection, which suggested that 5 mg/ml dose may be ideal[14]. Since intralesional injection on hair loss on the

eyebrow has a risk of development of cataract or glaucoma, careful attention is needed. Additional studies are needed on the appropriate dose and duration of treatment considering patients' factors such as location of hair loss, patients' age, and severity. Overall efficacy of topical corticosteroid in promoting hair growth ranged from 46.9% to >80%, and that of TA-intralesional injection was between 60% and >80%; furthermore, the side effects were tolerable. Based on the evidence of efficacy and safety profile, the use of topical steroid or TA-intralesional injection is recommended alone or together in adult AA patients.

2) Topical corticosteroid or intralesional corticosteroid injection for pediatric AA patients

We recommend use of topical corticosteroid for pediatric patients with AA (LOR: 2b, GOR: B, AR: 98.0%).

We conditionally recommend intralesional corticosteroid injection for pediatric patients with AA (LOR: 4, GOR: C, AR: 24.5%).

The efficacy data of topical corticosteroid monotherapy in pediatric AA was assessed by analyzing 65 reported cases [19-23], including two RCTs (n=19 and 41, respectively). Among these 65 patients, hair growth was observed in 42 (64.6%) patients, although the regimen was variable. Pascher et al.[20] proved the efficacy of topical fluocinolone acetate compared to vehicle in 19 pediatric patients with AA or alopecia totalis (AT) through a split scalp comparison. Adverse effects of topical corticosteroid included folliculitis and skin atrophy. Additionally, Lenane et al.[21] performed an RCT to compare the efficacy of high-and low-potency topical corticosteroid in pediatric patients with AA. A higher proportion of patients who received clobetasol propionate 0.05% cream once a day for 24 weeks achieved $SALT_{50}$ (defined as 50% regrowth using SALT) (17/20, 85.0%), compared to hydrocortisone 1% cream (7/21, 33.3%). Only one out of 20 patients with topical clobetasol propionate reported skin atrophy.

We found only one low-quality cohort study assessing the efficacy of intralesional injection in pediatric AA patients. Among 280 pediatric AA patients with TA-intralesional injection, the $SALT_{50}$ achievement rate was 75.4% (211/280) at 24 weeks. However, TA-intralesional injection was stopped in 11.4% (32/280) of children due to pain or lack of efficacy[24]. The use of topical corticosteroid as a first-line treatment for pediatric patients with AA is well supported. However, considering the potential side effects, such as pain, skin atrophy, and hyperpigmentation, intralesional injection should be considered conditionally.

3) Topical calcineurin inhibitor for adult AA patients

We conditionally recommend the use of topical calcineurin inhibitor for adult patients with AA (LOR: 2b, GOR: C, AR: 26.5%).

We found only one RCT investigating the efficacy of topical calcineurin inhibitor compared to placebo[25]. Ucak et al.[25] randomly divided adult AA patients into the following groups: 1) topical clobetasol propionate 0.05% (n=30), 2) topical pimecrolimus 1% (n=30), 3) petrolatum (n=20), 4) split scalp with topical clobetasol propionate 0.05% and pimecrolimus 1% (n=20). In their study, the efficacy of topical pimecrolimus was found to be superior to that of placebo and not inferior to clobetasol propionate. Although other studies failed to demonstrate the efficacy of topical calcineurin inhibitor in AA patients[12,26-28], significant proportion of subjects had long standing refractory AA in several studies. As topical calcineurin inhibitor is tolerable, it may be used in adult patients with AA who are treatment-refractory or have side effects of topical corticosteroid.

4) Topical calcineurin inhibitor for pediatric AA patients

We conditionally recommend the use of topical calcineurin inhibitor for pediatric patients with AA (LOR: 4, GOR: C, AR: 24.5%).

To date, there have been only a few case series and prospective split studies assessing the efficacy of topical calcineurin inhibitor in pediatric AA patients. Jung et al. reported that only 1/3 patients (33.3%) showed partial improvement with tacrolimus[22]. Similarly, Rigopoulos et al.[26], Price et al.[27], and Thiers[29] reported poor efficacy of topical pimecrolimus or tacrolimus. A recent systematic review of seven pediatric patients reported that 71% of patients showed no response or aggravation, and no treatment-related adverse effects were observed[30]. However, Sotiriou et al.[31] observed significant hair growth in 5/11 pediatric AA patients (44%) after 6 months of tacrolimus treatment. Furthermore, Bimbi et al.[32] reported complete hair growth in a child with AT after occlusion of tacrolimus. The evidence to recommend topical calcineurin inhibitor in pediatric AA is inconsistent so far.

5) Topical calcipotriol treatments for AA patients

We conditionally recommend the use of topical calcipotriol for adult patients with AA (LOR: 2b, GOR: C, AR: 16.3%).

There have been two retrospective cohort studies and one prospective intra-individual split study assessing the effectiveness of topical calcipotriol treatments for AA patients[33-35]. Narang et al.[35] treated 22 AA patients with calcipotriol lotion 0.005% twice a day; 59.1% of these patients demonstrated hair regrowth at 12 weeks. Molinelli et al.[33] compared the efficacy of topical calcipotriol 0.005% and clobetasol 0.05% in 35 patients with mild to moderate AA, and the regrowth score was not significantly different. These results suggest that topical calcipotriol can be considered in refractory cases or in patients experiencing adverse effects of topical corticosteroid.

6) Topical minoxidil for adult AA patients

We conditionally recommend topical minoxidil for patients with AA (LOR: 2b, GOR: C, AR: 81.6%).

A total of 10 articles, including two systematic reviews, were found[36,37]. When 1% minoxidil ointment or lotion was used in 30 adult patients with AA, 73.3% and 80.8% of the treatment group responded after 3 and 6 months after application, respectively. However, among nine patients with AT or alopecia universalis (AU), only two patients (22.2%) responded[38]. In another study, 30 AA patients were treated with 3% liquid minoxidil or placebo for 12 weeks; the two groups did not demonstrate significant differences. Furthermore, no response was observed in AT or AU patients[39]. Similarly, in the other two studies, AT or severe AA patients (SALT≥50) did not show a significant response to 3% or 5% minoxidil compared to placebo[40,41]. Although there were no significant differences in the effectiveness depending on the minoxidil concentration, the treatment effect tended to last longer when the concentration was high[42]. Skin irritation, including prickling and itching, has been reported as a temporary adverse effect. It is difficult to determine the definite therapeutic effect of topical minoxidil monotherapy because of inconsistent results, particularly in patients with severe AA.

7) Topical minoxidil for pediatric AA patients

We conditionally recommend topical minoxidil for pediatric patients with AA (LOR: 4, GOR: C, AR: 81.6%).

A total of 10 related articles, including four systematic reviews, were found in the literature covering topical minoxidil use in pediatric AA patients[19,30,37,43-49]. Most of these were case reports or series, wherein minoxidil was applied once or twice a day with varying concentrations (1%~5%), and the patient age ranged between 2~14 years[43-48]. One study revealed that topical minoxidil monotherapy was more effective compared to placebo[50]. However, some studies have shown that hypertrichosis occurs with or without hair growth during minoxidil application[48,51]. Since there are no controlled studies assessing the effects of topical minoxidil in children with AA, further research is required. In addition, children may be particularly vulnerable to the side effects of topical minoxidil, such as hypertrichosis.

8) Prostaglandin analogs for AA patients

We conditionally recommend topical prostaglandin analogues for patients with AA of eyelashes (LOR: 2b, GOR: C, AR: 65.3%).

Among 44 adult AU patients treated with 0.005% latanoprost on eyelashes daily for 2 years, 45% showed cosmetically acceptable regrowth. No regrowth was observed in the control group[52]. In another study, among 37 AA patients with involved eyelashes who applied 0.03% bimatoprost daily for a year, 70% showed eyelash regrowth[53]. Additionally, there have been several reports on the efficacy of topical prostaglandin analogues in pediatric AA involving the eyelashes (age range: 5~17 years)[54-58]. However, there were also several studies with negative results[59-61]. For example, 26 patients with symmetrical eyelashes and eyebrow AAs were treated for over 4 months with topical latanoprost. Only one patient showed partial hair regrowth on the treated side[60]. Similarly, when latanoprost or bimatoprost was applied for 16 weeks in 11 AA patients with 50% or more bilateral eyelash loss, there was no hair growth on either side in all the patients[61]. As spontaneous recovery cannot be excluded and most reports are limited to case studies, further work is needed.

9) Contact immunotherapy for adult AA patients

We recommend contact immunotherapy for adult patients with AA (LOR: 2a, GOR: B, AR: 73.5%).

We analyzed 56 studies[50,62-116] describing the efficacy of contact immunotherapy using diphenylcyclopropenone (DPCP), squaric acid dibutylester (SADBE), and dinitrochlorobenzene. Among the studies that used negative controls, all trials compared the efficacy of contact immunotherapy by applying it on

the half side of the scalp[16,18,19,21,25,26,28,43,49,50,67,69,70,77,79,80,82,86,87,89,109] except for one RCT[50].

Jang et al.[117] conducted a systematic review of 26 studies that reported the clinical efficacy of DPCP-based contact immunotherapy. Overall, 53.75% (95% confidence interval [CI], 52.20%~55.30%) of all treated patients and 47.65% (95% CI, 44.34%~50.96%) of severe patients with AT/AU showed significant hair regrowth, respectively. Among 15 studies reporting adverse events, severe eczematous reactions (20%), lymphadenopathy (13.5%), generalized eczematous reactions (8.5%), hyperpigmentation (6.8%), severe pruritus (6.4%), and hypopigmentation (1.6%) were common adverse events after the contact immunotherapy. Lee et al.[118] performed a meta-analysis of 45 studies that evaluated the efficacy of contact immunotherapy using DPCP or SADBE in 2,227 patients with AA. The overall rate of any hair regrowth was 65.5% among all treated patients; of these, 32.3% showed complete regrowth, defined as hair regrowth covering more than 90% of the scalp. Treatment-related adverse effects included severe eczema (30.8%), lymphadenopathy (25.7%), generalized eczema (15.8%), hyperpigmentation (12.7%), and influenza-like symptoms (11.1%).

Despite paucity of well-designed, controlled trials, clinical evidences support the recommendation of contact immunotherapy for adult AA.

10) Contact immunotherapy using DPCP for adult patients with severe AA

We recommend contact immunotherapy using DPCP for adult patients with severe AA (LOR: 2b, GOR: B, AR: 91.8%).

The definition of severe AA is heterogeneous among the studies, i.e., SALT>40% or 50%, or AT/AU. In a meta-analysis conducted by Lee et al.[118], the overall regrowth rate was 74.6% in patchy alopecia and 54.5% in the AT/AU subgroups (odds ratio [OR], 3.05; 95% CI, 2.26~4.12).

Gupta et al.[119] conducted a network meta-analysis. They defined clinical improvement as cases that experienced hair regrowth of more than 75% or at a cosmetically acceptable level. A meta-analysis of the DPCP-based contact immunotherapy[50,69,79,80,82,87,89,109] revealed an OR of 2.35 (95% CI, 0.76~7.21) for clinical improvement in mild cases and 48.36 (95% CI 20.93~111.76) in moderate and severe AA. Similarly, SADBE-based contact immunotherapy[50,67,70,77,86] was also found to induce clinical improvement in moderate and severe AA (OR, 25.34; 95% CI, 4.02~159.74). However, a network meta-analysis using the surface under the cumulative ranking curve favored DPCP-based contact immunotherapy[119].

Two prospective studies comparing the efficacies of DPCP and SADBE[50,103] did not show consistent results. Furthermore, because of inconsistent protocols for contact immunotherapy across studies, no significant difference in therapeutic effects between the two sensitizers could be concluded[120-122].

Clinical evidence supports the recommendation of contact immunotherapy to treat patients with severe AA. Thus far, there has been no conclusive evidence supporting which sensitizer affords the best clinical efficacy. However, DPCP, a sensitizer more commonly available in domestic clinical settings, is preferentially recommended in Korea.

11) Contact immunotherapy for pediatric AA patients

We recommend contact immunotherapy for pediatric patients with AA (LOR: 2b, GOR: B, AR: 79.6%).

The efficacy of contact immunotherapy in pediatric patients has been studied in small case series and uncontrolled cohort studies[50,70,75,81,85,90,91,95,96,99-101,104,110,123]. The treatment protocol varied significantly among the studies. Recently, a systematic review reported that 54% out of 351 pediatric patients with AA showed significant hair regrowth after contact immunotherapy using either DPCP or SADBE[19]. In another systematic review, the ratio of participants who showed successful complete regrowth has been broadly reported between 0% to 33.3%[30]. Based on the evidence on the efficacy of contact immunotherapy in pediatric patients with AA, contact immunotherapy can be recommended to pediatric AA patients. However, there have been no comparative studies that included controls for contact sensitizers in children, and further RCTs are required.

12) Topical anthralin for refractory AA patients

We conditionally recommend topical anthralin for patients with refractory AA (LOR: 4, GOR: C, AR: 18.4%).

Topical anthralin or dithranol has been used as an alternative to contact immunotherapy against AA. Inconsistent response rates between 0 to 75% have been reported after topical anthralin monotherapy; however, a few trials conducted with a negative control arm favor clinical benefits of topical anthralin treatment[124,125]. Although the efficacy of topical anthralin alone is not superior to contact immunotherapy

using DPCP[126], there are a few studies suggesting that topical anthralin can be beneficial in patients refractory to contact immunotherapy or in combination with contact immunotherapy[71,127].

13) Topical Janus kinase inhibitor for AA patients

While Janus kinase (JAK) inhibitors are promising options for treatment, and their topical use to minimize the potential adverse effects of systemic administration is attractive, the results are not yet been consistent. In a study by Bokhari et al.[128], 2% tofacitinib, 1% ruxolitinib, 0.005% topical clobetasol dipropionate, and vehicle (placebo) were applied for 28 weeks on the four scalp areas of 16 patients with AU, respectively. Partial hair regrowth was observed in the tofacitinib (6/16), ruxolitinib (5/16), and clobetasol (10/16) groups, but not in the placebo group (0/16). In a study by Olsen et al.[129], the first open label study of 12 patients with AA with a mean baseline SALT score of 56.2 revealed that 50% of subjects achieved $SALT_{50}$ at 24 weeks with 1.5% ruxolitinib cream. However, in the second RCT study, the proportion of $SALT_{50}$ achievers at 24 weeks was the same between the group receiving 1.5% ruxolitinib (baseline mean SALT=59.0, n=39) and the vehicle group (baseline mean SALT=59.9, n=39) (12.8% vs. 12.8%). In the study of Putterman et al.[130], 11 children aged 4~16 years of age (initial SALT 15~100) were treated with 2% topical tofacitinib for 12~76 weeks, and SALT score was decreased 32.3% in average. Additionally, $SALT_{50}$ was achieved in 3/11 (27.2%), and any hair regrowth was observed in 8/11 (72.7%).

Device-based treatment

A total of five statements for various device-based treatments for AA were developed (Table 3), and a consensus was achieved in one out of five statements (20.0%).

1) Excimer Laser

We conditionally recommend excimer laser treatment for patients with AA (LOR: 3a, GOR: C, AR: 49.0%).

Lee et al.[131] performed a meta-analysis using nine prospective trials with 129 patients[16,132-139]. In five controlled clinical trials, considerable improvements were observed in the excimer group compared to the untreated control (relative risk 7.83; 95% CI: 2.11~29.11).

A recent systematic review of pediatric AA patients showed that excimer laser resulted significant improvement in 58.8%.[30,132-134,140] Further validation via adequately powered RCTs is needed.

2) Narrowband UVB (NBUVB)

Several clinical studies have reported variable results for NBUVB[15,141-144]. In an RCT, the NBUVB treatment group showed a statistically significant (p=0.037) improvement in SALT score compared to placebo[142]. However, in most other previous case series, the therapeutic effect of NBUVB was reported to be inferior to that of other therapies[15,141,143]. Additionally, in a case series of six children, 83.3% (5/6) showed insufficient improvement[144].

3) Cryotherapy

We conditionally recommend cryotherapy for patients with

Table 3. Evidence-based statement and expert consensus of device-based treatment

Statement	Level of evidence	Strength of recommendation	Percentage of participants with score ≥7	Average agreement score (range)	Consensus
We conditionally recommend excimer laser treatment for patients with AA.	3a	C	49.0	6.3	
We conditionally recommend cryotherapy for patients with AA.	3b	C	38.8	6.2	
We conditionally recommend microneedling as a combination therapy for patients with AA.	4	C	12.2	4.6	
We conditionally recommend platelet-rich plasma intralesional injection for patients with AA.	2b	C	16.3	4.6	
We recommend using wigs or hair prostheses for patients with recalcitrant AA.	4	C	93.9	8.3	Yes

AA: alopecia areata.

AA (LOR: 3b, GOR: C, AR: 38.8%).

In an RCT involving 240 patients randomized to cryotherapy or TA-intralesional injection (5 mg/ml), the response rate was 56.7% in cryotherapy and 83.3% in the intralesional injection group[17]. Jun and Lee[145] performed a scalp-split study using cryotherapy and a 0.25% prednicarbate solution and hair growth was more pronounced in the cryotherapy group. In another study, 11 patients with recalcitrant AA to various treatments for 6 months responded to cryotherapy after 5 weeks of treatment[146]. Although cryotherapy appears to have therapeutic potential[17,145-155] more studies are needed to prove its effectiveness.

4) Microneedling

We conditionally recommend microneedling as combination therapy for patients with AA (LOR: 4, GOR: C, AR: 12.2%).

Only a few retrospective studies have been conducted assessing the efficacy of microneedling.Most studies used combination treatments with topical steroid preparations[156-158], platelet-rich plasma[159,160], or photodynamic therapy[161,162] and reported that combination treatment demonstrated better efficacy over microneedling monotherapy alone.

5) Platelet-rich plasma

We conditionally recommend platelet-rich plasma intralesional injection for patients with AA (LOR: 2b, GOR: C, AR: 16.3%).

Five RCTs[163-167] have so far been conducted assessing the efficacy of platelet-rich plasma. For example, Kapoor et al.[166] randomly treated 40 patients with patchy AA using platelet-rich plasma or TA-intralesional injection (10 mg/ml) four times and found both treatments as effective. Despite these promising results, more studies are required to evaluate efficacy and to standardize the treatment protocols.

6) Stem cell therapy

Several case-control studies and case series have been conducted assessing the efficacy of stem cell therapy[168-171]. In 52 patients, mesenchymal stem cells were found to be effective in promoting hair growth.

7) Fractional erbium yttrium aluminum garnet (Er:YAG) laser

In a case series, 7 recalcitrant AA patients treated with Er:YAG laser showed hair regrowth[172]. In a controlled trial, the outcome of a combination of topical minoxidil and fractional:Er:YAG laser was better than that of topical minoxidil alone[173].

8) Low-level laser therapy

In a controlled trial which used infrared diode laser to treat patchy AA in 16 patients, complete or partial regrowth was observed in 94% of treated patches, while no growth was observed in patches left untreated[174].

9) Hair prosthesis (wig, hairpiece)

We recommend using wigs or hair prostheses for patients with recalcitrant AA (LOR: 4, GOR: C, AR: 93.9%).

In a systematic review and meta-analysis that evaluated health-related quality of life in patients with AA, wearing wigs had a positive impact[175]. In a Korean cross-sectional study, wigs had a positive effect on psychosocial aspects in patients with severe AA, as proven by the objective parameter Psychosocial Impact of Assistive Device Scale[176]. Based on evidences, the use of wigs and hair prostheses has positive effect on psychological aspect and quality of life of AA patients. Although the LOR is low due to the difficulty of designing well-controlled RTC using wigs, the committee reached a consensus regarding a strong recommendation in favor of the use of wigs in AA patients who do not respond to the therapies considering that recalcitrant AA has a great impact on quality of life of the patients.

DISCUSSION

Although the prognosis of AA is difficult to predict, patients with less severe disease at presentation are more likely to be free of disease at follow-up (68% of AA patients with SALT less than 25%; 32% with SALT 25%~50%; 8% with SALT more than 50% at presentation)[177]. Additionally, patients with limited area of alopecic patches frequently experience spontaneous recovery without specific treatment[178]. Thus, topical treatment with relatively low risk of adverse events remains the mainstay in patients with limited patchy hair loss, whereas more proactive or systemic treatment may be required to treat patients with extensive AA.

There was lack of high-quality RCT data on the topical and device-based treatment. However, there was clear expert consensus on several modalities. Especially, the vast majority

of experts agreed to contact immunotherapy, which is a strong call for the urgent legitimation. Also, hair prostheses are very important and medical or financial support for these devices are required.

The present study provides up-to-date, evidence-based treatment guidelines for AA based on the consensus reached among experts after considering regional healthcare circumstances, adding diversity to the previous guidelines.

ACKNOWLEDGMENT

We appreciate the active participation and guidance from the KHRS council members in developing the guidelines.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

FUNDING SOURCE

This work was supported by the Korean Hair Research Society (KHRS).

DATA SHARING STATEMENT

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

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