Original Article | Annals of Dermatology 2023;35(3):205-216 • https://doi.org/10.5021/ad.22.167

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Guidelines for the Management of Patients with Alopecia Areata in Korea: Part II Systemic Treatment

Hyunsun Park, Jung Eun Kim[1], Jee Woong Choi[2], Do Young Kim[3], Yong Hyun Jang[4], Young Lee[5], Jiehyun Jeon[6], Hyun-Tae Shin[7], Min Sung Kim[8], Jung Won Shin[9], Sung Bin Cho[10], Bark-Lynn Lew[11], Gwang Seong Choi[7]

Department of Dermatology, SMG-SNU Boramae Medical Center, Seoul, Korea; [1]Department of Dermatology, College of Medicine, The Catholic University of Korea, Seoul, Korea; [2]Department of Dermatology, Ajou University School of Medicine, Suwon, Korea; [3]Department of Dermatology, Yonsei University College of Medicine, Seoul, Korea; [4]Department of Dermatology, School of Medicine, Kyungpook National University, Daegu, Korea; [5]Department of Dermatology, School of Medicine, Chungnam National University, Daejeon, Korea; [6]Department of Dermatology, Guro Hospital, Korea University College of Medicine, Seoul, Korea; [7]Department of Dermatology, Inha University School of Medicine, Incheon, Korea; [8]Department of Dermatology, School of Medicine, Chosun University, Gwangju, Korea; [9]Department of Dermatology, Seoul National University Bundang Hospital, Bundang, Korea; [10]Yonsei Seran Dermatology and Laser Clinic, Seoul, Korea; [11]Department of Dermatology, Kyung Hee University School of Medicine, Seoul, Korea

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

Corresponding Author
Bark-Lynn Lew
Department of Dermatology, Kyung Hee University Hospital at Gangdong, 892 Dongnam-ro, Gangdong-gu, Seoul 05278, Korea
Tel: +82-2-440-7329
Fax: +82-2-440-7336
E-mail: bellotte@hanmail.net
https://orcid.org/0000-0003-4443-4161

Background: Alopecia areata (AA) is a chronic disease with an unpredictable course and can have a severe psychological impact on an individual.
Objective: To provide evidence and consensus-based statements regarding the treatment of patients with AA in Korea.
Methods: We searched for relevant studies from inception to May 2021 regarding the systemic treatment of AA. 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 statement, and an agreement of 75% or greater was considered as having reached consensus.
Results: Current evidence supports the efficacy of systemic corticosteroids, oral cyclosporine monotherapy or combination with systemic corticosteroids, and oral Janus kinase inhibitors in severe AA patients. Systemic steroids may be considered for pediatric patients with severe AA. A consensus was achieved in three out of nine (33.3%), and one out of three (33.3%) statements pertaining to systemic treatment in adult and pediatric AA, respectively.
Conclusion: The present study produced up-to-date, evidence-based treatment guidelines for AA associated with the consensus obtained by experts based on the Korean healthcare system.

Keywords: Alopecia areata, Guideline, Korea, Systemic, Therapeutics, Treatment

INTRODUCTION

Alopecia areata (AA) is a chronic disease with an unpredictable course and can have a severe psychological impact on an individual. Since the release of the Korean Hair Research Society (KHRS) guidelines for treatment of AA in 2011, there has been a growing demand for new guidelines based on updated clinical evidence. Thus, current guidelines have been prepared to incorporate up-to-date clinical evidence-based recommendations and treatment algorithms tailored to the circumstances in Korea. This is the second part of the series on systemic AA treatment. Possible indicators of poor prognosis at the presentation include development of multiple discrete patches, extensive hair loss involving >50% of the scalp, and progression to alopecia totalis (AT) or alopecia universalis (AU)[1]. Previous guidelines suggest that there is rationale and expert consensus to treat extensive AA with active systemic treatment in attempt to arrest disease progression and to reverse hair loss[1-5].

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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.

The method in detail is described in the first part of the series. A systematic literature search (PubMed, Korean Med, Cochrane library, and Scopus databases) was conducted from inception to May 30, 2021, using a combination of search terms, "alopecia areata," "child," "pediatric," "systemic," "steroid," "corticosteroid," "cyclosporine," "azathioprine," "sulfasalazine," "simvastatin/ezetimibe," "inosiplex," "inosine pranobex," "Isoprinosine," "antihistamine," "ebastine," "fexofenadine," "levocetirizine," "Janus kinase inhibitors," "JAK inhibitor," "ruxolitinib," "baricitinib," "tofacitinib," "ritlecitinib," "brepocitinib," "biologics," "efalizumab," "alefacept," "abatacept," and "interleukin." This systematic literature review was registered with PROSPERO (CRD42021250392) and was exempted from obtaining approval from the institutional review board (07-2021-30). The members primarily evaluated the evidence behind each statement, and the strength of the recommendations was classified according to Table 1[6].

A total of 51 out of 60 board members of the KHRS participated in the three discrete rounds of online voting.

RESULTS

Systemic treatment

A total of 12 statements were developed for various systemic treatments for AA, and a consensus was achieved for a total of four out of 12 statements (25.0%) (Table 2).

Systemic corticosteroids for severe adult AA patients

We recommend oral corticosteroids for adult patients with severe AA (level of evidence: 2b, grade of recommendation: B, agreement rate: 91.8%).

Only one randomized controlled trial (RCT) has investigated the therapeutic effect of systemic steroids against AA in a study containing a placebo control group[7]. This study included 43 patients with severe AA. Among them, 23 patients received oral prednisolone (200 mg once weekly) for 3 months, and 20 patients received placebo for 3 months. In the prednisolone treatment group, 3 out of 23 patients dropped out, and eight out of 20 (40.0%) showed significant hair regrowth (≥31% hair regrowth). Of the eight patients with significant hair regrowth, two showed complete hair regrowth, and recurrence was observed in two patients. In the control group, 4 out of 20 dropped out, and 16 patients underwent a final evaluation; no significant hair regrowth was observed (0%) in this study. Other randomized studies have compared different steroid regimens without placebo controls[8,9]. Although not RCTs, there are case series that reported the efficacy of systemic steroid monotherapy[10-22]; however, it is difficult to generalize the results due to the heterogeneous regimens among these studies. In a recent Alopecia Areata Consensus of Experts (ACE)

Table 1. Level of evidence and strength of the recommendations

Strength of recommendation		Level of evidence	
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

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 systemic treatment

Statement	Level of evidence	Strength of recommendation	Percentage of participants with score ≥7	Average agreement score	Consensus
We recommend systemic corticosteroids for adult patients with severe AA.	2b	B	91.8	7.9	Yes
We conditionally recommend systemic corticosteroids for pediatric patients with severe AA.	4	C	75.5	6.7	Yes
We recommend cyclosporine monotherapy or in combination with systemic corticosteroids for adult patients with severe AA.	3a	B	91.8	7.9	Yes
We conditionally recommend cyclosporine for pediatric patients with severe AA.	4	C	73.5	6.4	
We conditionally recommend azathioprine monotherapy or combination with corticosteroid for patients with severe AA.	2b	C	14.3	4.8	
We conditionally recommend methotrexate monotherapy or combination with corticosteroid for patients with severe AA.	4	C	30.6	5.4	
We conditionally recommend sulfasalazine monotherapy or combination with corticosteroid for patients with severe AA.	4	C	10.2	4.1	
We conditionally recommend simvastatin/ezetimibe for patients with severe refractory AA.	4	C	18.4	4.3	
We conditionally recommend inosiplex for patients with refractory AA.	2b	C	10.2	3.9	
We conditionally recommend antihistamines for patients with AA.	3b	C	28.6	4.7	
We recommend oral JAK inhibitor for adult patients with severe AA.	1b	B	83.7	7.5	Yes
We conditionally recommend oral JAK inhibitor for pediatric patients with severe AA.	4	C	49.0	6.0	

AA: alopecia areata, JAK: Janus kinase.

study published in 2020, there was a clear consensus on the use of oral steroids as first-line treatment for severe (SALT>50) adult AA and daily administration of prednisolone (or prednisone) was the preferred choice[3]. In addition, an initial dose of 0.4 to 0.6 mg/kg/day with gradual tapering over more than 12 weeks was suggested by consensus. However, there are studies suggesting that pulse corticosteroid therapy is superior to daily oral corticosteroid therapy in terms of therapeutic effect and adverse effect profile[8,23,24]. For example, in a study where steroid administration was randomized into three groups (oral prednisolone pulse therapy vs. oral dexamethasone daily administration vs. intramuscular triamcinolone acetonide monthly administration), the overall relapse rate was significantly lower in the oral prednisolone pulse therapy group, compared to that in the oral dexamethasone daily administration group[8]. Thus, further studies are necessary on the mode of administration. Additionally, the previous study which investigated the prognosis of patients who received pulse corticosteroid therapy for more than 10 years, patients with AT and AU demonstrated poor short-term and long-term prognosis[25].

Systemic corticosteroids for severe pediatric AA patients

We conditionally recommend oral corticosteroids for pediatric patients with severe AA (level of evidence: 4, grade of recommendation: C, agreement rate: 75.5%).

In a systematic review published in 2021 regarding the treatment of AA in children[26], systemic steroids were found to be effective in 72.9% (102/140) patients. However, the therapy had the highest recurrence rate (62.9%, 61/97 patients) among various other treatment options. Oral prednisolone

pulse therapy (5 mg/kg or 300 mg once a month) or sustained therapy (0.5~2 mg/kg/day or 5~10 mg/day), intravenous methylprednisolone pulse therapy (8~30 mg/kg for three days once a month or 500 mg for one day once a month) is used frequently. Although side effects do not appear frequently, various side effects such as weight gain, acne, muscle pain, headache, abdominal pain, behavior change, Cushing's syndrome, increased intraocular pressure, menstrual irregularity, and hirsutism have been reported.

Another systematic review analyzed 272 pediatric AA patients[27] receiving various therapies, including intravenous pulse-dosed corticosteroids, oral pulse-dosed corticosteroids, oral corticosteroid maintenance or tapered therapy, intramuscular corticosteroids, as well as combination therapy with cyclosporine and methotrexate (MTX). According to this study, although doses and cycles varied depending on the route of steroid administration, 45% (0%~100%) of patients receiving intravenous or oral pulse-dosed corticosteroids and 34% (0%~100%) of patients receiving traditional oral corticosteroid regimens (0%~55.5%) showed a complete response. The recurrence rate was 16.7%~100% for pulse-dosed corticosteroids and 50%~100% for non-pulse-dosed traditional oral corticosteroid regimens. The studies reported significant adverse events, including weight gain, infection, hypertension, Cushing's symptoms, psychiatric disorders, striae, and acne, and these adverse events occur more frequently in non-pulse regimens. Considering significant adverse events and frequent relapse, systemic corticosteroid is conditionally recommended in pediatric patients with severe AA.

The age range of the pediatric patients included in the previous 28 reports on children varied from 1 to 18 years, and the age distribution in each study was highly heterogeneous. A recent ACE study[3] reported that oral corticosteroids are one of the most appropriate treatment for acute severe AA (SALT>50) in children (7 years and older); however, no consensus was reached for the use of oral corticosteroid in children younger than 6 years, regardless of SALT.

Oral cyclosporine for severe adult AA patients

We recommend cyclosporine monotherapy or in combination with oral corticosteroids for adult patients with severe AA (level of evidence: 3a, grade of recommendation: B, agreement rate: 91.8%).

Only one RCT investigated the therapeutic effect of cyclosporine in severe AA[28]. This double-blind, randomized, placebo-controlled design included 32 adults aged 18~65 with moderate-to-severe AA. Patients were randomized to receive cyclosporine (4 mg/kg/day) or a placebo for 3 months. The rate of achieving $SALT_{50}$ was higher (31.3%) in the cyclosporine group, compared to the placebo group (6.3%), with marginal statistical significance (p=0.07). The authors suggested that cyclosporine monotherapy was moderately effective in inducing remission in patients with moderate-to-severe AA.

A meta-analysis reporting the therapeutic effect of cyclosporine in AA was published in 2021[29]. Seven studies were included to analyze cyclosporine monotherapy and eight studies for systemic corticosteroid combination therapy. In this study, "responder" was defined as a case showing terminal hair regrowth of more than 50%. The proportion of overall mean responders was 73% (95% confidence interval [CI], 57%~85%). The mean recurrence rate was 39% (10%~78%). The authors concluded that cyclosporine has a positive therapeutic effect on AA. Additionally, the mean proportion of responders to cyclosporine monotherapy was 66% (50%~79%) and 78% (48%~93%) for systemic corticosteroid combination treatment. The recurrence rate was 55% (6%~96%) for monotherapy and 28% (6%~72%) for combination, respectively[29]. The daily dose of cyclosporine alone was 4.71±1.05 mg/kg. The dose of cyclosporine decreased to 3.1±0.83 mg/kg during systemic corticosteroid combination treatment. Similarly, in another systematic review, the combined treatment showed superior therapeutic effect (69% vs. 57%) and a lower recurrence rate than monotherapy (36% vs. 73%)[30]. Additionally, some studies reported that systemic cyclosporine and low-dose corticosteroid combination therapy for severe AA have led to high response rates and steroid-sparing effects[31-33].

Although the recent RCT and meta-analysis demonstrated positive result on the therapeutic effect of cyclosporine for severe AA in adults, some of the included studies have limitations and requires further studies. As oral cyclosporine for severe AA can be reimbursed by National Health Insurance program in Korea, it may partially explain the relatively high consensus rate of oral cyclosporine for severe AA in the present study.

Oral cyclosporine for severe pediatric AA patients

We conditionally recommend cyclosporine for pediatric patients with severe AA (level of evidence: 4, grade of recommendation: C, agreement rate: 73.5%).

Although studies have shown that cyclosporine is effective in treating AA in children, there have been no related RCTs illustrating the same. In a systematic review on the treatment of AA in children[26], 32 patients with severe AA in three studies[33-35] were included. The analysis included patients receiving cyclosporine monotherapy, as well as systemic steroids and psoralen ultraviolet A treatment in combination with cyclosporine. The dose of cyclosporine was 100~200 mg/day or 5~7.5 mg/kg/day. The response rate for cyclosporine monotherapy was 83.3% (5/6 patients), the global response rate was 59.4% (19/32 patients), and the recurrence rate was 100% (5/5 patients). No adverse effects were observed. Considering there are only a few studies with small number of patients, oral cyclosporine may be conditionally used for severe refractory AA in children.

Oral azathioprine for severe AA patients

We conditionally recommend azathioprine monotherapy or combination with corticosteroid for patients with severe AA (level of evidence: 2b, grade of recommendation: C, agreement rate: 14.3%).

Most studies investigating oral azathioprine for severe AA patients were uncontrolled[36-41]. Gupta et al.[37] published an open-label RCT of weekly azathioprine pulse therapy (WAP, 300 mg/week) and betamethasone oral mini-pulse therapy (OMP, 5 mg×2 days every week) in 50 participants (SALT>10). At 4 months, 44.52% in WAP and 71.43% in OMP groups, respectively, showed hair growth. Previous studies have included heterogeneous groups of patients with variable treatment regimens, making it challenging to generalize the results. Side effects include elevated liver enzymes, leukopenia, nausea, vomiting, abdominal discomfort, pancreatitis, and bone marrow suppression.

Saoji et al.[41] treated pediatric AA patients (age 2~13 years) with azathioprine (1 mg/kg/day) who experienced side effects after using oral corticosteroids. Most patients showed hair regrowth, and there were no side effects during the use of azathioprine for 6 to 8 months. However, data in terms of the risk and benefit of using azathioprine remain insufficient.

Oral methotrexate for severe AA patients

We conditionally recommend MTX monotherapy or combination with corticosteroid for patients with severe AA (level of evidence: 4, grade of recommendation: C, agreement rate: 30.6%).

A recent meta-analysis[42] result showed that, overall, the proportion of complete response (100% hair regrowth) to MTX in AA was 35.8% (95% CI 25.0%~48.3%). In a subgroup analysis, complete response in adult studies was 44.7% (32.9%~57.1%) compared with 11.6% (5.1%~24.5%) in the pediatric population. The rate of complete response was significantly higher in the adult cases (p=0.001).

Phan et al.[43] reported a retrospective chart review involving 10 cases of pediatric AA patients treated with MTX, along with a meta-analysis and literature review[44-48]. The meta-analysis showed a good overall regrowth (>50% hair regrowth), with complete regrowth in 49.7% (95% CI 37.8%~61.7%) cases. The relapse rate was 30% (17%~47.2%). Although adverse reactions occurred in 15.7% (8.0%~28.5%) of cases, these were mostly mild.

In a systemic review published by Barton et al.[27] that analyzed the course of 42 patients, complete response was noted in 17.9% (range 0%~50%) of patients, and partial response in 47.9% (range 0%~100%). The dosage was 2.5 mg to 25 mg/week (0.2 mg/kg/day).

A literature search for treatment of AA with MTX revealed that most individual studies were small case series and additional research is needed.

Oral sulfasalazine for severe AA patients

We conditionally recommend sulfasalazine monotherapy or combination with corticosteroid for patients with severe AA (level of evidence: 4, grade of recommendation: C, agreement rate: 10.2%).

Most studies on the use of oral sulfasalazine for severe AA patients were case series and uncontrolled open-label prospective studies[49-52]. The largest study was conducted by Rashidi and Mahd[52], which reported the efficacy of sulfasalazine in 39 patients (seven pediatric patients) with recalcitrant AA. The starting dose in their study was 1 g/day, which was increased to 3 g/day after three months of therapy, and was continued for six months. The terminal hair regrowth was quantified as 1%~29% (no response or a weak response), 30%~59% (moderate response), or 60%~100% (good to excellent response). Ten patients (25.6%) showed good responses, and moderate hair regrowth was noted in 12 patients (30.7%). There was no response in 17 patients (43.5%). Side effects that occurred during treatments included dizziness and headache in two patients,

which were resolved by lowering the dose of sulfasalazine. Dyspepsia in eight patients was treated using antacids.

A recent meta-analysis[27] reported limited evidence supporting the use of sulfasalazine and mesalazine for the treatment of pediatric AA and additional studies are needed in the future.

Oral simvastatin/ezetimibe

We conditionally recommend simvastatin/ezetimibe for patients with severe refractory AA (level of evidence: 4, grade of recommendation: C, agreement rate: 18.4%).

We found nine reports of oral simvastatin/ezetimibe against AA; simvastatin and ezetimibe were administered in combination in all these reports. These reports included case reports, case series, and case-control studies. No single RCT was found. Furthermore, case-control studies included only a small number of subjects[53] and showed conflicting outcomes with study results[54,55].

In a case of pediatric AA patients, one study reported the use of simvastatin/ezetimibe in a 6-year-old girl with refractory AU who had experienced treatment failure with previously administered systemic prednisolone and contact diphenylcyclopropenone therapy[56]. In this case report, near-complete remission was achieved after administering systemic prednisolone and minoxidil combined with simvastatin/ezetimibe administration.

Oral inosiplex

We conditionally recommend inosiplex for patients with refractory AA (level of evidence: 2b, grade of recommendation: C, agreement rate: 10.2%).

Five research papers on the administration of inosiplex to AA were searched[57-61]. The most recent RCT related to inosiplex was published in 2006[60]. Thirty-two treatment-resistant AA patients were randomized to receive inosiplex 50 mg/kg/day and placebo for 12 weeks. The results of the 29 patients were analyzed. Five out of 15 patients receiving inosiplex showed complete hair growth, and eight showed partial response, indicating statistically significant differences compared to the placebo groups.

Since other drugs and treatment modalities are medically preferable for AA, administering inosiplex can only be considered as an alternative treatment option.

Oral antihistamine

We conditionally recommend antihistamines for patients with AA (level of evidence: 3b, grade of recommendation: C , agreement rate: 28.6%).

There were no RCTs on the use of oral antihistamines to treat AA, and most studies were either case series or case reports[57-60]. A retrospective study stated that administering fexofenadine enhanced the effectiveness of contact immunotherapy in 121 patients with extensive AA lesions[62]. In AA patients with atopic background, the mean reduction in SALT score in the fexofenadine group was 1.333 (n=33) and that of the control group was 0.471 (n=34) (p=0.00213). However, further studies are required as the results do not appear clinically meaningful.

Oral JAK inhibitors for severe adult AA patients

We recommend oral JAK inhibitor for adult patients with severe AA (level of evidence:1b, grade of recommendation: B, agreement rate: 83.7%).

Previously, there had been retrospective case series and open-label prospective trials without a placebo control group. A systematic review and meta-analysis in 2019[63] and in 2020[64] that collectively analyzed treatment outcomes of oral and topical JAK inhibitors reported a good response (more than 50% improvement in SALT) in 54.0% and 45.7% of patients, respectively. Furthermore, no serious adverse effects were observed. In a meta-analysis from 2021[65] based on 12 studies involving six or more adult patients, a total of 346 patients were analyzed. Of these, 288 patients were treated with oral tofacitinib, and 58 were treated with oral ruxolitinib. Overall, $SALT_{50}$ was achieved in 66.0% of patients treated with oral JAK inhibitors. Infections, including upper respiratory tract infection, urinary tract infection, and herpes zoster, were the most common side effects. However, there were no serious side effects such as malignancy. Some of these studies reported a recurrence rate and nearly 74% of patients experienced recurrence 3 months after drug discontinuation.

The results of a phase 2a randomized, placebo-controlled trial randomized trial involving ritlecitinib and brepocitinib were published in 2021[66]. In this study, adults with severe AA with ≥50% scalp hair loss received ritlecitinib (n=48), brepocitinib (n=47), and placebo (n=47). At 24 weeks of drug administration, the mean difference from placebo in SALT score change from baseline was 31.1 (95% CI, 18.8~43.5) and

49.2 (36.6~61.7) (p<0.0001 for both drugs compared to placebo) in the ritlecitinib and brepocitinib groups, respectively. Adverse events were reported in 32/48 (66.7%), 36/47 (76.6%), and 35/47 (74.5%) patients in the ritlecitinib, brepocitinib, and placebo groups, respectively. The most common side effects were upper respiratory tract infections, nasopharyngitis, headache, acne, and nausea. The drug was discontinued owing to side effects in 4%, 9%, and 6% of patients. Two patients in the brepocitinib group developed rhabdomyolysis; however, all patients experienced rhabdomyolysis after heavy physical activity and recovered without sequelae.

Promising results are consistently reported in systematic reviews or meta-analyses of retrospective and prospective observational studies with oral JAK inhibitors and an individual RCT. Therefore, we recommend oral JAK inhibitor for adult patients with severe AA.

Oral JAK inhibitors for severe pediatric AA patients

There were five studies on oral JAK inhibitors in children, none of which were placebo-controlled RCTs. All of them were retrospective case series. Four studies were finally selected[67-71] that included children with severe AA, and the available data were used to calculate the proportion of $SALT_{50}$ achievers. Among children/adolescents (ages 4~19 years) with severe AA, $SALT_{50}$ was achieved in 82% of cases. All patients received tofacitinib; however, the daily dose was different in each study (2.5~10 mg). Most studies did not specifically mention side effects, and data on recurrence after discontinuation were unavailable, as most patients were taking the drug continuously. In one study, adverse events were mainly reported to be transient and mild, with the elevation of liver enzymes and eosinophilia being the most common.

AA can lower self-esteem and cause severe mental stress, especially in children and adolescents. Although the existing literature comprises mostly small-scale retrospective observational studies on oral JAK inhibitors in children and adolescents with AA, favorable outcomes have been reported repeatedly. However, further research is required to confirm this hypothesis, as data are still lacking on the appropriate drug dosage and potential side effects associated with long-term use.

Biologics

Studies with biologics included one RCT employing efalizumab[72], one RCT using alefacept[73], one open-label study of interleukin-2[74], one open-label study of abatacept[75], and several case reports or case series that reported the use of dupliumab, ustekinumab, and secukinumab. Among these, efalizumab and alefacept are no longer commercially available. Furthermore, interleukin-2, abatacept, and secukinumab did not lead to significant hair growth. Similarly, dupilumab or ustekinumab are difficult to be considered as effective agents because the outcomes after their use have remained inconsistent.

DISCUSSION

Currently, there is scarce RCT data regarding the available systemic therapies for AA are not adequate to help choose the medications to support choices, which is also reflected by the low consensus rate in this study. Despite these limitations, some AA treatment modalities have demonstrated promising results in various studies with consistent outcomes or are supported by the consensus from the majority of expert panels. Based on the investigation from part I (topical and device-based treatment) and part II (systemic treatment), the current guidelines suggest treatment algorithms for the management of AA (Fig. 1). Some patient groups require special consideration. For example, severe AA generally has a lower response to treatment, demonstrates unpredictable course, and often requires long-term treatment in many cases. Additionally, for children with age under 12 years of age, clinicians are less confident in selecting appropriate treatment options. Thus, the present algorithms aimed to offer practical guidelines for a number of cases with various conditions, such as 1) severe AA (SALT>50), 2) pediatric patients with age ≤12 years, and 3) AA refractory to the first-line treatment. Although pediatric AA represents approximately 18.1% of AA patients of all ages and has significant psychosocial impact[76], therapeutic options are limited. The recent consensus treatment guidelines of 50 AA experts, mostly from North America and Europe, mentioned that safety concerns have precedence over treatment efficacy in children irrespective of disease severity, and systemic therapy may be considered as first-line treatment in adolescents (aged 13~18 years) and in adults presenting with severe disease. Considering these points, options without a high agreement rate but with some evidence may also be conditionally considered for pediatric patients with severe refractory AA as second-line treatment following an individualized assessment of risk and benefit. However, since there are only a few

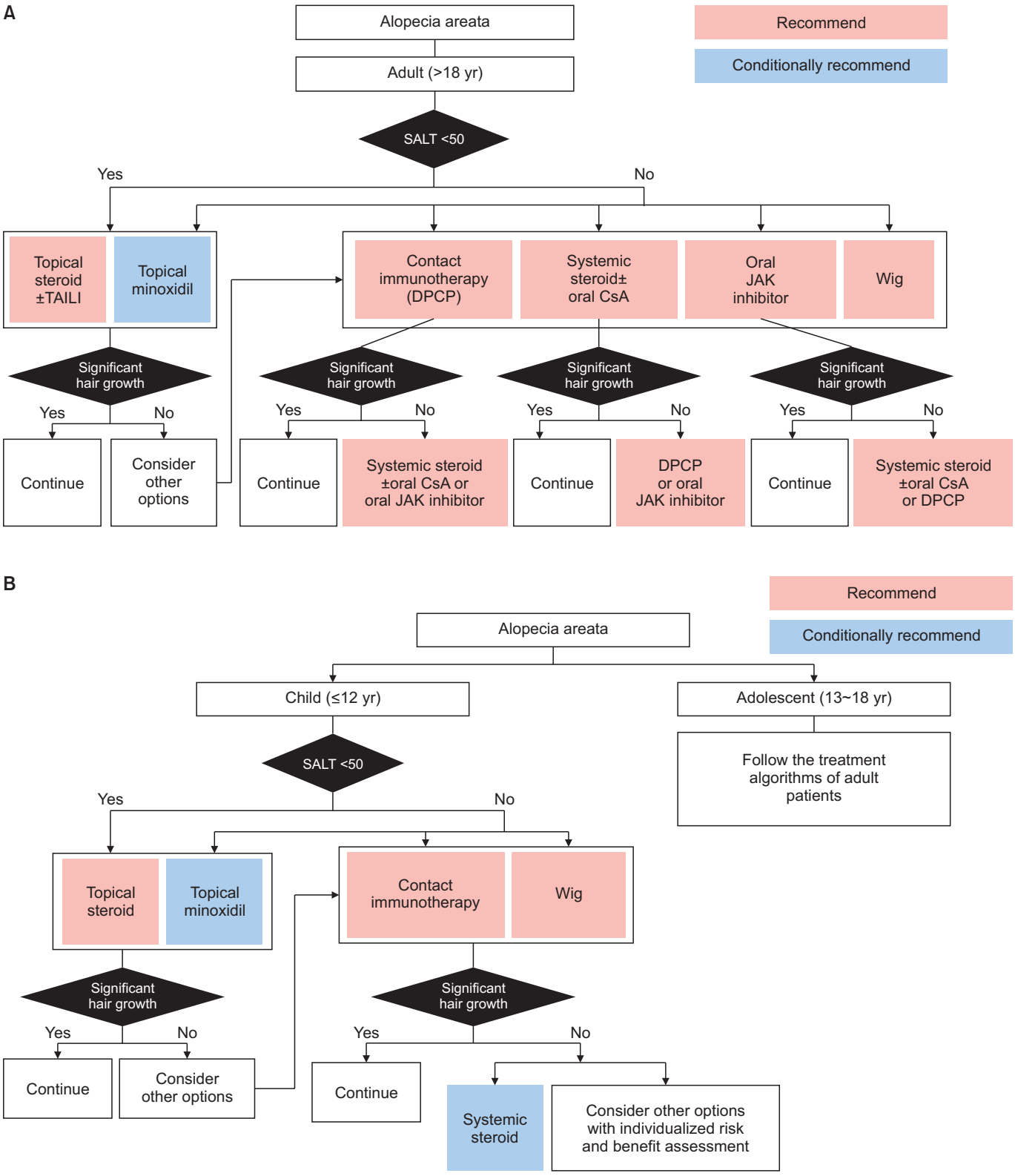

Fig. 1. Treatment algorithms for the management of alopecia areata according to the severity and patient age (A) algorithms for adult (B) algorithms for child and adolescent. Significant hair growth: cosmetically acceptable hair growth (SALT<20). SALT: the Severity of Alopecia Tool score, DPCP: diphenylcyclopropenone.

studies and no globally accepted consensus on the minimum age at which different AA treatments are to be recommended, including systemic, topical AA treatment, or contact immunotherapy, further studies are required to explore this aspect. Among the AA treatment modalities included in the present algorithm, no option had been approved by the US FDA, yet. However, a phase 3 large-scale RCT data (n=1,200) was very recently published and reported the efficacy and safety of baricitinib for treatment of severe AA[77], leading to the US FDA approval of baricitinib for AA treatment.

The present study has potential limitations. The statements did not include all the available AA treatment modalities. Expert consensus is from the single country reflecting reginal specificity and may not be generalized. Some specific groups, such as patients with active or chronic AA were not explored. Most importantly, there are lack of high quality RCTs in therapeutics for AA, and further studies are required. In spite of these limitations, the present study is valuable considering that the previous guidelines are mostly from western societies and may underrepresent ethnic or regional minorities[1,3,4,78-80]. The present guideline from different background and health care system can add diversity to achieve better care for AA patients. Furthermore, although contact immunotherapy is widely accepted in many countries and recommended as the first-line alternatives in various guidelines[1,3,4], it is unfortunately unavailable in Korea. Also, wigs and hair prostheses are very important to improve the quality of life and relieve psychological impact of patients with AA. However, the patients with AA do not have medical or financial support for these devices in Korea, increasing psychological and financial burden of the patients. There is an urgent need for legitimation and institutional strategy to support their use.

The present study produced up-to-date, evidence-based treatment guidelines to treat AA based on the consensus between experts within the Korean healthcare system, which will help the clinicians to set up treatment strategy.

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.

ORCID

Hyunsun Park, https://orcid.org/0000-0003-1338-654X
Jung Eun Kim, https://orcid.org/0000-0003-1670-0995
Jee Woong Choi, https://orcid.org/0000-0003-4631-7823
Do Young Kim, https://orcid.org/0000-0002-0194-9854
Yong Hyun Jang, https://orcid.org/0000-0003-1706-007X
Young Lee, https://orcid.org/0000-0001-9205-1785
Jiehyun Jeon, https://orcid.org/0000-0003-2456-7573
Hyun-Tae Shin, https://orcid.org/0000-0003-1799-5860
Min Sung Kim, https://orcid.org/0000-0002-8102-6653
Jung Won Shin, https://orcid.org/0000-0003-1166-0189
Sung Bin Cho, https://orcid.org/0000-0001-6748-5071
Bark-Lynn Lew, https://orcid.org/0000-0003-4443-4161
Gwang Seong Choi, https://orcid.org/0000-0002-5766-0179

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