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REVIEW ARTICLE

European expert consensus statement on the systemic treatment of alopecia areata

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Abstract

Alopecia areata is an autoimmune form of non-scarring hair loss. It is usually characterized by limited areas of hair loss. However, the disease may progress to complete scalp and body hair loss (alopecia *totalis*, alopecia *universalis*). In patients with alopecia areata hair loss significantly impacts the quality of life. Children and adolescents with alopecia areata often experience bullying, including physical aggression. The disease severity evaluation tools used in clinical practice are: the Severity of Alopecia Tool (SALT) score and the Alopecia Areata Scale (AAS). A SALT score equal to or greater than 20 constitutes a commonly accepted indication for systemic therapy in alopecia areata. When using the AAS, moderate to severe alopecia areata should be considered a medical indication for systemic treatment. Currently, the only two EMA-approved medications for alopecia areata are baricitinib (JAK 1/2 inhibitor) for adults and ritlecitinib (JAK 3/TEC inhibitor) for individuals aged 12 and older. Both are EMA-approved for patients with severe alopecia areata. Other systemic medications used off-label in alopecia areata include glucocorticosteroids, cyclosporine, methotrexate and azathioprine. Oral minoxidil is considered an adjuvant therapy with limited data confirming its possible efficacy. This consensus statement is to outline a systemic treatment algorithm for alopecia areata, indications for systemic treatment, available therapeutic options, their efficacy and safety, as well as the duration of the therapy.

INTRODUCTION

Alopecia areata is an autoimmune form of hair loss associated with the loss of immune privilege in the hair follicle. The lifetime risk of the disease is estimated to range from 0.7% to 3.8%.[1]

The disease creates a significant burden for the patients and their families. It is associated with an increased risk of anxiety and depression. Up to 62% of patients with alopecia areata make major life decisions including relationships, education and career based on their alopecia areata.[2] Children and adolescents with hair loss often experience bullying, also physical aggression. Both children and adults with alopecia areata are commonly considered suffering from cancer or are undergoing chemotherapy.[2]

Alopecia areata may occur at any age. In many cases, it begins in childhood. It is estimated that 40% of patients experience their first episode of hair loss by the age of 20 and 83%–88% by the age of 40 years.[3] It was reported that the development of alopecia areata after the age of 50 is associated with a less severe course and better prognosis.[4]

Alopecia areata is characterized by the presence of hairless areas within the skin that remains normal and is devoid of inflammatory signs.[5] Clinically, various patterns of hair loss may be observed: patchy, ophiasis (band-like hair loss in the parieto-temporo-occipital area), ophiasis *inversa*—sisaipho (hair loss in the fronto-parieto-temporal area), reticular and diffuse.[6] Moreover, alopecia *totalis* (complete scalp hair loss) and alopecia *universalis* (complete scalp and body hair loss) are observed in 7%–12% of cases.[7]

Autoimmune comorbidities of alopecia areata include thyroiditis, celiac disease, vitiligo, type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus and myasthenia gravis.[8] Associations between alopecia areata and atopic diseases, such as atopic dermatitis, asthma, allergic rhinitis and allergic conjunctivitis are well-documented.[9] Recent studies have shown that alopecia areata may be associated with an increased risk of developing hypertension, hyperlipidemia, obesity, metabolic syndrome and cardiovascular diseases.[10,11]

DIAGNOSIS AND BASELINE EXAMINATION

The diagnosis of alopecia areata is established on the basis of clinical examination and trichoscopic findings. In atypical cases, a histological examination of a 4 mm scalp biopsy may be helpful.[5] A trichoscopy-guided biopsy should include areas indicative of high disease activity (exclamation mark hairs, tapering hairs, black dots).[12] If not present, then the hair-bearing margin of the patch is a preferable biopsy area. Investigation for comorbidities is based on medical history and clinical findings. Additional tests also include those needed to exclude contraindications for the intended therapy.[13]

ASSESSMENT OF THE SEVERITY OF HAIR LOSS

The severity of alopecia areata is most commonly assessed by the Severity of Alopecia Tool (SALT). The SALT score reflects the area of scalp hair loss. It may be given either in absolute numbers, or percentages, for example, SALT = 10 or SALT 10% means that 10% of scalp surface is hairless. Both variants are correct.[14] The classification of alopecia areata severity based on the SALT score is presented in Table 1. In 2022, King et al.[15] proposed a new Alopecia Areata Scale (AAS) which is not limited to the affected scalp area and comprises other aspects of disease severity (Table 2).

THERAPEUTIC MANAGEMENT

Indications for the systemic therapy of alopecia areata

A SALT score equal to or greater than 20,[16] corresponding to moderate to severe alopecia areata, is considered a general medical indication for systemic therapy.[17] When using the AAS, moderate to severe alopecia areata would usually require systemic therapy.[17]

Some experts indicate a possible discordance of the recommended medical indications with available data from double-blind, randomized, controlled, multicenter, trials and with European Medicines Agency (EMA) approvals, which are limited to severe alopecia areata for Janus Kinase (JAK) inhibitors (baricitinib and ritlecitinib) and not existing for other available systemic treatment options.

Therapeutic options

Oral glucocorticosteroids

There is no consensus on the preferred glucocorticosteroid and the recommended dose.[18] Australian[19] and Saudi[13] experts recommended prednisolone at the initial dose of 0.5–0.75 mg/kg/day and 0.4–0.6 mg/kg/day, respectively. Pulse therapy with glucocorticosteroids may also be considered, for example, dexamethasone administered at a dose of 0.1 mg/kg/day on two consecutive days per week for several months.[19,20] No comparative studies tackled the issue of the efficacy and safety of continuous versus pulsed therapy. Intramuscular triamcinolone acetonide (up to 40 mg once a

TABLE 1 Severity of Alopecia Areata Tool (SALT) score.

Scalp alopecia areata	SALT score
Mild	≤20
Moderate	21–49
Severe	≥50

Note: A simplified classification method.

TABLE 2 Alopecia Areata Scale (AAS).

	Scalp hair loss	SALT score
1	Mild	≤20
2	Moderate	21–49
3	Severe	≥50

If mild or moderate, increase AA severity rating by one level if one or more of the following additional criteria is present:

Additional criteria:
- noticeable involvement of eyebrows or eyelashes,
- inadequate response after at least 6 months of treatment,
- diffuse (multifocal) positive pull test consistent with rapidly progressive alopecia areata,
- negative impact on psychosocial functioning resulting from alopecia areata.

week) is also used in some countries in the treatment of alopecia areata.[16] The use of intravenous methylprednisolone in pulses, currently is not recommended by most experts because of a low durability of the therapeutic effects.[19] The use of systemic glucocorticosteroids in monotherapy should be limited to patients in whom combined therapy is impossible or contraindicated.[16] Also, a course of systemic glucocorticosteroids in monotherapy may be considered as an initiation therapy in patients with active alopecia areata.

Cyclosporine

Cyclosporine may be used as monotherapy or in combination with glucocorticosteroids. Recent systematic reviews, encompassing over 300 reported cases demonstrated that the combined therapy with cyclosporine plus systemic glucocorticosteroids was superior to cyclosporine monotherapy with a clinical response observed in 69.4% and 57.0% of patients, respectively, both with a good safety profile.[21,22] However the high variability in patient characteristics, treatment regimen and definition of treatment response makes it difficult to draw a definitive conclusion from the available studies.[21] Treatment duration ranged from 2 to 36 months. The recurrence rate was 36.1% and 73.91%, respectively.

The usual dose of cyclosporine in the treatment of alopecia areata varies from 3 to 5 mg/kg/day.[13] The dose of 5 mg/kg/day should not be exceeded, because of the increased risk of nephrotoxicity. Lower doses (i.e. below 2 mg/kg/day) were also reported to be effective.[23] Most experts indicate that treatment with cyclosporine should typically not exceed about 12 months.[13,16] Taken into consideration the limitations in dosing, the safety profile is good if the patient and the healthcare provider adhere to appropriate monitoring.

Methotrexate

Methotrexate may be used as monotherapy or in combination with oral glucocorticosteroids in alopecia areata. It can be administered subcutaneously or orally. The typical dose ranges from 15 to 25 mg/week[16,19] for both ways of administration.

There are significant discrepancies in the reported efficacy of methotrexate in alopecia areata. In a randomized multicenter clinical study[24] that included 89 patients with alopecia *totalis* or alopecia *universalis*, complete or near complete regrowth (SALT < 10) was observed in only 2% of patients receiving methotrexate (25 mg/week) after 12 months of treatment and in 0% of patients receiving placebo. Combination treatment with methotrexate (25 mg/week) and prednisone (15–20 mg/day) resulted in regrowth to SALT <10 in 20%–31% of patients. Another recent retrospective study conducted on 26 patients indicates that combining methotrexate (5–20 mg/week) with methylprednisolone (up to 32 mg/day) shows a therapeutic effect comparable to methylprednisolone alone.[25] This may suggest no added value from methotrexate. However, other retrospective studies in smaller groups of patients may indicate that the therapeutic effect is possible to achieve in 38%–50% of patients treated with methotrexate in monotherapy[26–28] and in 57%–77% of patients treated with methotrexate in combination with glucocorticosteroids.[25,27–31] This variability of results and subsequent discrepancy in conclusions about the possible efficacy of methotrexate in alopecia areata may result from different definitions of therapeutic response by different authors and the insufficient amount of data from prospective clinical trials.

The safety profile is good if methotrexate is administered with folic acid at the dose of 15 mg/week or more (usually 15–30 mg/day) and both the patient and the healthcare provider monitoring adhere to adequate monitoring.

Azathioprine

Azathioprine is a less investigated treatment option for alopecia areata.[32] It is usually used as a steroid-sparing agent.[13,19] The drug is usually started at a low dose of 0.5–1 mg/kg/day to reduce the risk of gastrointestinal problems. It is gradually titrated every 4–6 weeks, reaching the maximum dose rate of 2–3 mg/kg/day based on patient response and tolerance. It is recommended to monitor thiopurine methyltransferase (TPMT) activity prior to treatment and modify the dose depending on TPMT activity. Azathioprine may be combined with oral glucocorticosteroids.[19,32]

JAK inhibitors

JAK inhibitors are small-molecule drugs that have become the mainstay of treatment in numerous autoimmune diseases, including alopecia areata.[16] The following JAK inhibitors have been studied in alopecia areata.

Baricitinib (JAK 1/2 inhibitor)

Baricitinib is the first medication approved by the EMA and the Food and Drug Administration (FDA) for the

treatment of severe alopecia areata in adults (patients aged ≥18 years).

The efficacy of baricitinib in alopecia areata was confirmed in two completed phase 3 randomized clinical trials (BRAVE-AA1 and BRAVE-AA2) involving 1200 patients with severe alopecia areata (SALT >50).[33] At week 36, 38.8% of patients treated with baricitinib 4 mg/day achieved SALT = 20 compared to 22.8% of patients treated with 2 mg/day and 6.2% of patients receiving placebo.

The Summary of Product Characteristics (SmPC) recommends the use of baricitinib at a dose of 4 mg/day. A dose of 2 mg once daily may be appropriate for patients aged ≥75 years and for patients with a history of chronic or recurrent infections. A dose of 2 mg once daily may also be considered for patients who have achieved sustained control of disease activity with 4 mg once daily and are eligible for dose tapering and maintenance therapy.

When treating with baricitinib, the EMA safety measures for JAK inhibitors have to be taken into consideration (see below for details).

Ritlecitinib (JAK 3/TEC inhibitor)

Ritlecitinib is approved by the FDA and EMA for the treatment of severe alopecia areata in adults and adolescents 12 years of age or older. It is a selective dual inhibitor that blocks JAK 3 and TEC. The efficacy of ritlecitinib in alopecia areata has been documented in phase 2a[34] and 2b-3[35] randomized, placebo-controlled clinical trials. With 200 mg/day ritlecitinib loading dose (four weeks) and continued therapy with 50 mg/day, $SALT_{30}$ (30% SALT improvement) was achieved by 50% of patients and $SALT_{90}$ by 25% in the phase 2a clinical trial.[34] In the phase 2b-3 trial[35] ritlecitinib has shown following the efficacy. At week 24, 31% of patients in the ritlecitinib 200 mg/50 mg group, 23% of patients in the ritlecitinib 50 mg group and 2% in the placebo group had a positive response based on a SALT score of 20 or less. An increased efficacy was demonstrated with ongoing treatment during the 48-week observation period. Regrowth of eyebrows and eyelashes was observed.[36] When responders were switched to placebo and then back to ritlecitinib upon relapse, only 57% of patients responded to the second course of ritlecitinib. These observations may indicate that in patients who have a good therapeutic effect, treatment should not be discontinued too early.[37]

The EMA-approved dose of ritlecitinib is 50 mg/day. As indicated in the SmPC, laboratory monitoring should include platelet count and lymphocyte count. Consideration should be given to discontinuing ritlecitinib in patients who show no evidence of therapeutic benefit after 36 weeks. The EMA general safety measures for JAK inhibitors do not include ritlecitinib as of December 2023.

Other JAK inhibitors

Other JAK inhibitors were used off-label in alopecia areata, including tofacitinib (JAK 1/3 inhibitor) at a dose of 2 × 5 mg/day, ruxolitinib (JAK 1/2 inhibitor) at a dose of 2 × 20 mg/day, upadacitinib (JAK 1 inhibitor) at a dose of 30 mg/day as well as delgocitinib (JAK 1-3/TYK2) in Japan at a dose of 30 mg/day. Brepocitinib at a dose of 30–60 mg/day (TYK2/JAK1 inhibitor), deuruxolitinib at a dose of 2 × 8 mg/day are at various pre-approval stages of drug development for alopecia areata.[38,39]

Safety profile of systemic JAK inhibitors in alopecia areata

Recent systematic reviews show that the safety profile of JAK inhibitors in alopecia areata in both adults[40,41] and children[42] is good.

The most common side effects of JAK inhibitors in patients with alopecia areata are headache and acne. The odds ratio for upper respiratory tract infections varies from over 7-fold increased to comparable to placebo depending on the JAK inhibitor. The risk of serious adverse events is not increased.[41]

A phase 3b/4 randomized safety trial clinical trial (ORAL *Surveillance study*) performed in patients with rheumatoid arthritis aged ≥50 years with one or more cardiovascular risks has shown that in this population adverse effects from tofacitinib are more common compared to TNF inhibitors (either adalimumab or etanercept).[43] On the basis of those results, and a later analysis of specific subpopulations from this study the EMA recommended in 2023 that JAK inhibitors (tofacitinib, baricitinib, upadacitinib, abrocitinib, filgotinib) should be used in the following patients only if no suitable treatment alternatives are available: those aged 65 years or above, those at increased risk of major cardiovascular problems (such as heart attack or stroke), those who smoke or have done so for a long time in the past, and those at increased risk of cancer. Cautious use is also recommended in patients with known risk factors for venous thromboembolism other than those listed above. An earlier recommendation by the FDA required warnings ('black box warning') about an increased risk for serious heart-related events, cancer, blood clots and death for JAK1 inhibitors (tofacitinib, baricitinib and upadacitinib).

It is worth emphasizing that some experts expressed their concern that the above announcements were based on the results obtained in one study, in one disease (rheumatoid arthritis), in one group of patients (50+ patients with cardiac risk factors) and compared to TNF inhibitors, which have a cardioprotective effect.

Available data show that in patients with alopecia areata adverse effects are usually mild and transient and that there is no increased risk of severe adverse effects compared to placebo.[42]

Moreover, patients with alopecia areata are generally younger and healthier, without comorbidities that increase the risk of side effects, as they were observed in patients with rheumatoid arthritis in the ORAL *Surveillance study*. However, until further studies are available, the EMA recommendations should be taken into consideration when initiating treatment and the patients should be appropriately monitored.

Other therapeutic options

Low-dose oral minoxidil may be considered as adjuvant therapy in patients with alopecia areata.[44] There is limited data on its efficacy in inducing hair regrowth in alopecia areata. Thus, it should not be used in monotherapy. Vitamins and other dietary supplements have no therapeutic significance in alopecia areata.[16] There are no official European recommendations in this regard. The FDA issued a recommendation not to use biotin in patients with hair loss unless there is a documented biotin deficiency.

'Wait-and-see' approach

Historically, a 'wait-and-see' approach has been suggested by some authors. However, the regrowth rate in the placebo group (defined as ≥50% of hair regrowth in patients not receiving active treatment) in severe alopecia areata is uncommon, ranging from 0% to 16.7%. Taken into account: the low chance of spontaneous regrowth, the level of ≥50% of hair regrowth not meeting current treatment goal criteria, and the better response to systemic therapy in patients with a shorter disease duration, the 'wait-and-see' approach is not advisable in patients qualifying for systemic therapy.

Therapeutic strategies

Systemic JAK inhibitors are the only group of officially approved medications for alopecia areata and their efficacy and safety in this condition are well documented in several randomized, placebo-controlled, clinical trials. This group of medications should be considered the first-choice therapeutic option in alopecia areata, with no preference in adults for either baricitinib or ritlecitinib (Figure 1). In children (aged ≥12 years) ritlecitinib is currently the only EMA-approved treatment.

It is advised to use systemic glucocorticosteroids as initiation therapy in patients with active alopecia areata (active hair loss of less than six months duration in treatment naïve patients). A combination therapy of JAK inhibitors with glucocorticosteroids was not investigated in large-scale studies, but available data indicate that this combination may result in an increased treatment efficacy.[45,46]

When JAK inhibitors are not available, not accessible or contraindicated, other systemic treatments should be considered (off-label). These include cyclosporine and methotrexate, with most authors recommending cyclosporine over methotrexate.

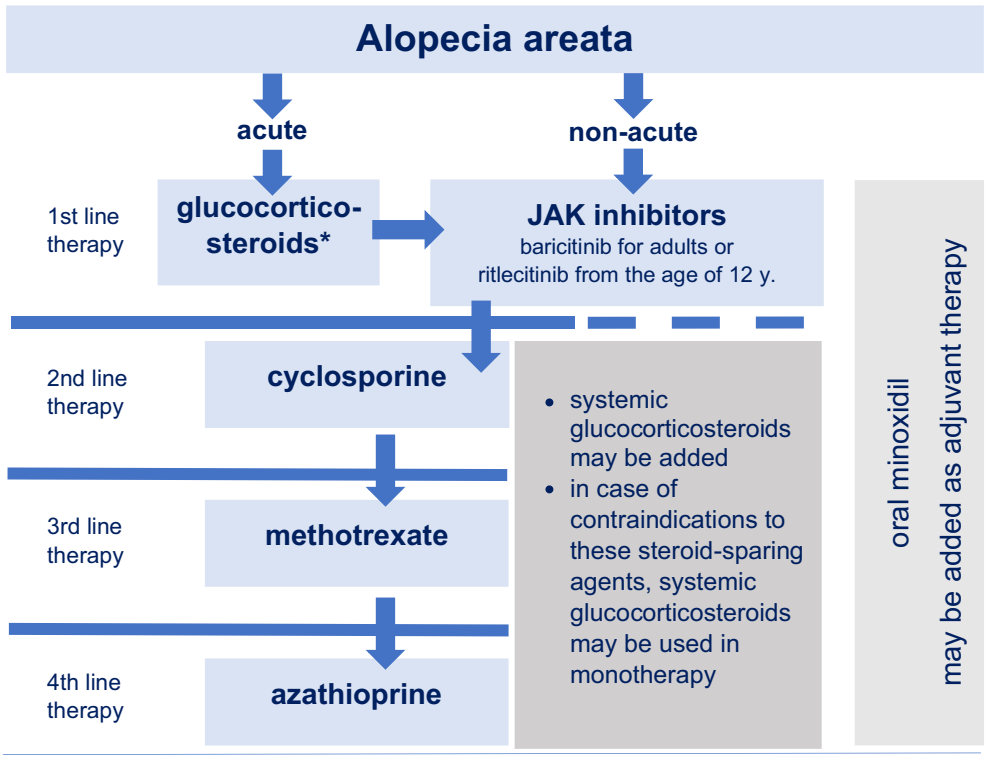

FIGURE 1 A suggested therapeutic algorithm for the systemic treatment of alopecia areata.

A similar treatment approach may be advisable for patients with beard alopecia areata, especially if loss of beard hair constitutes a significant psychological or social problem.

A suggested therapeutic algorithm for the systemic treatment of alopecia areata is presented in Figure 1. However, in every case, the treatment plan is established individually, depending on the patient's age, comorbidities, disease severity and activity, disease burden, prior treatments, physicians' preferences and current literature data, as well as the reimbursement regulations.

Therapeutic goals in alopecia areata

In recent years, SALT 20 has been defined as a therapeutic goal in patients with moderate and severe alopecia areata.[47] Currently, according to the predominant viewpoint, SALT of at least 10 or a 90% improvement in the SALT score should constitute the parameters reflecting successful treatment.[16]

A treatment switch or dose modification should be considered if the treatment goal is not achieved within 24–36 weeks.

Treatment duration and follow-up

The overall relapse rate in alopecia areata can be as high as 85%[48] and the next course of treatment may be less effective.[36] Thus, long-term maintenance therapy is very commonly required. There are no sufficient data to define the term 'long term' with expert opinions ranging from 3 to 7 years or even lifelong, as in many other autoimmune diseases.

Treatment duration with glucocorticosteroids should be limited if possible to reduce the risk of adverse events.[13,19]

To minimize the risk of relapses, treatment should ideally be continued for at least 6–12 months after complete hair regrowth,[16,19] before a possible switch to maintenance therapy or discontinuation. Detailed standards for maintenance therapy are still to be established and defined after specific clinical trials. The period between follow-up visits is dependent on the treatment regimen and ranges usually between one and few months.

Systemic treatment in children

Ritlecitinib is the only systemic treatment approved for alopecia areata in children from the age of 12 years. No medication has been approved for the treatment of alopecia areata in children below the age of 12.

If systemic treatment is required in children with alopecia areata aged 3–11, systemic glucocorticosteroids may be considered. According to an international expert consensus published in 2021,[49] oral glucocorticosteroids are recommended for children with acute disease from the age of seven and with SALT >30, and in chronic alopecia areata over the age of 13 years and with SALT >50.

Other therapeutic options in children with AA include tofacitinib (2.5–10 mg/day) or methotrexate 0.3–0.6 mg/kg/week. When considering cyclosporine for a child with alopecia areata, it has to be considered that literature data support the use of this drug from the age of six years, but unlike JAK inhibitors, cyclosporine is not centrally approved via a European procedure and approval conditions may vary between countries.

CONCLUSION

This consensus statement is based on the data published in the scientific literature, on the EMA and FDA documents as well as on clinical experience of dermatologists specialized in alopecia areata. It provides general information about systemic treatments available for adults and children. However, an individualized plan should always be established for every patient.

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DATA AVAILABILITY STATEMENT
Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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