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Treatment of Alopecia Areata and Its Numerous Possibilities: A Literature Review

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Abstract

Introduction and purpose: Alopecia Areata (AA) is an inflammatory autoimmune disorder characterized by non-scarring hair loss. While it is not life-threatening, it can lead to significant psychological distress. With advancements in modern medicine, new treatments, personalized therapies, and various therapeutic options have

emerged. The aim of this study is to review and assess the efficacy, outcomes, and side effects of the available treatment options.

Material and methods : To compile this article “PUBMED” and “Google Scholar” databases were used with the great attention given to the articles not older than the year 2018

Brief description of the state of knowledge: There are various treatment options for Alopecia Areata (AA), beginning with topical treatments such as corticosteroids, prostaglandin analogs, minoxidil, and contact immunotherapy. In more severe cases, systemic therapy, biological therapy, or alternative treatments should be considered.

Results and conclusions: In the treatment of mild Alopecia Areata (AA), topical therapies are the preferred option due to their minimal side effects and easy to apply nature, with corticosteroids demonstrating the best outcomes, particularly when used in combination therapies. In patients with moderate or severe AA, systemic therapies are recommended, alone or in combination with topical treatment. In patients resistant to other forms of therapy, biological treatments or less commonly used methods should be considered.

Keywords: Alopecia areata; treatment; dermatology; autoimmune diseases; quality of life

Introduction :

Alopecia areata (AA) is an inflammatory autoimmune disorder characterized by non-scarring hair loss, with preservation of the hair follicle. The condition affects both adults and children, and it can occur in individuals with or without a history of autoimmune diseases. It is worth noting that the prevalence of AA increases with age; thus, with rising life expectancy worldwide, the disease is becoming more common. The mean age of onset is 32 for males and 36 for females. Although data indicate no demonstrable sex predilection, alopecia areata is more frequently observed among Asian, Black, and Hispanic patients. While AA is not life-threatening, it often causes significant psychological distress, such as depression, anxiety, and mood disorders. The most common type of AA affects the scalp, though all hair-bearing areas can be involved. Despite its prevalence, most people are unaware of alopecia areata. Current research suggests that nearly 2% of the general population will experience it at some point in their lives. According to recent studies, AA appears to occur slightly more frequently in the pediatric population [1,2]. Advances in technology have enabled researchers to better understand the pathogenesis of AA. This progress has led to the development of new treatment regimens, tailored therapies, and numerous therapeutic options that were unavailable in the past. The aim of this study is to review and evaluate the efficacy,

therapeutic outcomes, and side effects of available treatment methods for alopecia areata in the general population. Additionally, strategies for preventing adverse effects associated with certain therapies are considered. Both traditional methods, which have been used for many years but do not always yield satisfactory results, as well as innovative and unconventional treatment approaches, are discussed.

Objective:

The aim of this study is to gather, present, and evaluate existing data from scientific articles on both pharmacological and non-pharmacological methods for treating alopecia areata.

Review Methodology:

To compile this article, literature on alopecia areata and its treatment regimens was reviewed. A literature search was conducted primarily using the PubMed and Google Scholar databases, with special attention given to articles published after 2018.

State of Knowledge – Pathogenesis, Diagnostic Criteria and available forms of treatment for Alopecia Areata

Pathogenesis

The physiological hair cycle consists of three stages: anagen, catagen, and telogen, which follow one another in sequence. During the anagen phase, the hair follicle maintains a state of immune privilege (IP), characterized by low expression of MHC proteins, minimal presence of inflammatory cytokines, and an absence of immune cells. In other words, this is a state where hair follicles are protected from attacks by the body's own immune system [1,3]. In areas affected by alopecia areata, there is increased expression of MHC class I molecules, which facilitates the influx of immune cells and subsequent damage to the hair follicle. CD4+ T lymphocytes, producing IFNγ and related cytokines, as well as cytotoxic CD8+ T lymphocytes, play a key role in the pathogenesis of AA. Their activity shortens the anagen phase and leads to an accelerated transition of the follicle to the telogen phase, resulting in hair loss [4]. Furthermore, gene expression profiling studies have shown that these T

lymphocytes and cytokines are significantly mediated by the JAK kinase pathway. Based on current medical knowledge, identifying a single, definitive cause for the onset of alopecia areata is often difficult; however, numerous trigger factors have been reported. The most common triggers include chronic emotional or physical stressors, such as injury or mental trauma. Additionally, some sources cite alopecia areata as an adverse event following immunization, particularly after vaccination against hepatitis B virus (HBV), Clostridium tetani, herpes zoster virus (HZV), or human papillomavirus (HPV) [1,5]. Oxidative stress is another important factor contributing to alopecia areata [6]. According to current scientific understanding, susceptibility to alopecia areata is highly complex and is thought to have a polygenic basis [7]. Researchers believe that the human leukocyte antigen class II (HLA-D) region of chromosome 6 plays a significant role in this susceptibility [8]. Additionally, gene expression profiling has shown that T lymphocytes and cytokines associated with interferon, which actively participate in the disease's pathogenesis, are largely mediated by the JAK kinase pathway. Numerous potential triggers for alopecia areata have been suggested in the medical literature [4].

Diagnostic Criteria

Although a diagnosis can often be made based on a physical examination, the gold standard is trichoscopic examination. In alopecia areata, some characteristic findings include "exclamation mark" hairs, which have a short hair shaft with a broader distal end. Other observable changes include triangular hairs, broken hairs, proximally tapered hairs, Pohl-Pinkus constrictions, [1,9] short vellus hairs, and the relatively characteristic, though not pathognomonic, yellow dots. [10] In diagnostically unclear cases, a skin biopsy is recommended. [11] In the early stages, biopsies from the edge of a bald patch may show lymphocytic infiltration around the hair bulb, including eosinophils, CD1+ and CD8+ cells. In established patches, hair follicles appear miniaturized, lying below the sebaceous gland level, predominantly in the early anagen stage. [1,11]

Progression is assessed using the Severity of Alopecia Tool (SALT) scale or the Alopecia Areata Scale. The SALT scale divides patients into five categories:

0 = no hair loss

1–20 = mild alopecia

21–49 = moderate alopecia

50–94 = severe alopecia

95–100 = very severe alopecia [12]

Patients with a SALT score of less than 20, or classified as having mild alopecia on the Alopecia Areata Scale, are typically candidates for treatment focused on topical therapies [12,13].

Types of Alopecia Areata:

Patchy AA: One or multiple patches of hair loss.

Alopecia Totalis: Total or near-total loss of hair on the scalp.

Alopecia Universalis: Total or near-total loss of hair on all body surfaces.

Alopecia Incognita: Diffuse hair loss, characterized by a positive pull test, the presence of yellow dots, and short, miniaturized regrowing hairs, without nail changes.

Ophiasis: Hair loss affecting the temporal, parietal, and occipital regions.

Sisaipho: Extensive hair loss sparing the peripheral region of the scalp.

Marie Antoinette Syndrome: An acute episode of diffuse alopecia with sudden loss of pigmented hair [1]

Topical Treatments

Corticosteroids: At the cellular level, glucocorticoids bind to the glucocorticoid receptor (GR) located in the cytoplasm. This complex then translocates to the nucleus, where it binds to specific DNA sequences known as glucocorticoid response elements (GREs). As a result, pro-inflammatory cytokine production is suppressed, and anti-inflammatory responses within the cell are activated. Additionally, glucocorticoids inhibit NF-kappaB, a protein complex that acts as a transcription factor, which plays a role in the pathophysiology of autoimmune diseases and chronic inflammatory processes. It is important to note that corticosteroids influence the inflammatory response not only at the transcriptional level but also by interacting with surface receptors on cells. Through this interaction and the release of secondary messenger signals, they suppress immune cells, including monocytes, T lymphocytes, and platelets [14]. Corticosteroids are recommended for patients with a short disease duration, less than 50% scalp involvement, and slowly progressing symptoms, or those with patchy-type alopecia [15]. The longer the disease duration, the less benefit is

derived from topical treatments._If no improvement is seen after six months, the treatment should be changed [14]. Corticosteroids can be administered in various forms. The most accessible options are topical steroids in the form of creams, foams, lotions, or sprays. This is a good option for patients who prefer not to use intralesional corticosteroids or those who cannot tolerate the pain associated with the procedure. Topical steroids are considered safer due to their lower complication rates and non-invasive nature, making them the first-line treatment in children [13]. It is advisable to choose strong steroids such as clobetasol propionate, betamethasone dipropionate, or fluocinolone acetonide. There is no significant difference in efficacy between these preparations [16]. Common side effects of this method include folliculitis and telangiectasia [17]. The relapse rate for this treatment method is between 37% and 63% [14]. To maintain the effects of steroid therapy, a treatment cycle of at least three months is recommended, along with maintenance therapy. Topical steroid use is not recommended in cases of alopecia totalis or universalis [18]. One possible modification of the application method is the use of occlusive therapy [19]. This has been shown to improve corticosteroid absorption and lead to clinical improvement in patients with alopecia universalis (AU) and alopecia totalis (AT) who were previously unresponsive to treatment. The effectiveness of 0.05% clobetasol propionate under occlusion has been demonstrated [20]. However, increased absorption also leads to systemic complications typical of corticosteroid use [21]. Another method is the intralesional administration of triamcinolone acetonide (TA), which is particularly recommended as a first-line treatment for patients with patch-type AA and those in the active phase of the disease, especially when a positive hair pull test and exclamation mark hairs are present. Studies have shown that intralesional corticosteroid injections, especially with triamcinolone acetonide, are effective in promoting hair regrowth in patients with alopecia areata. In one study, 71% of patients with subtotal alopecia experienced hair regrowth, compared to only 7% in the placebo group [19,22]. While intralesional therapy is recommended when less than 50% of the scalp is affected, there have been reports of its effectiveness in more advanced cases, though these involved small patient groups [23]. Various concentrations of triamcinolone are available, such as 2.5 mg/mL, 5 mg/mL, or 10 mg/mL. Available evidence suggests that while there is no significant difference in efficacy between concentrations, those ranging from 5-10 mg/mL appear to be more effective [24]. Unfortunately, long-term and high-concentration use of intralesional corticosteroids (IC) leads to side effects in approximately 24% of patients [14]. One notable side effect is skin atrophy at the injection site, which can be avoided by administering

injections deeper into the skin and limiting the volume of the product used [19]. Systemic complications related to intralesional corticosteroids are more common with this method. When comparing efficacy of topical steroids and intralesional steroids, the results are mixed. Many studies indicate comparable efficacy between the two methods in monotherapy, while others suggest the superiority of intralesional therapy [25]. In 2022, a study compared combined therapy (simultaneous use of intralesional and topical therapy) with monotherapy, finding no additional benefit for combined therapy over monotherapy [25].

Prostaglandin Analogs: Prostaglandin analogs such as latanoprost, bimatoprost, and travoprost were first studied in 2003, with experimental studies on macaques showing encouraging results. High concentrations of latanoprost resulted in moderate to marked hair growth on the scalp. The proposed mechanism of action is thought to be similar to that of minoxidil, stimulating prostaglandin E2 (PGE2) synthesis. The role of prostaglandin-H synthase (PGHS)-1 activation and prostaglandin receptors (EP3 and EP4) in hair follicle development and regrowth has been emphasized [26]. Prostaglandin analogs stimulate the anagen phase, increase hair density, and promote the transition from telogen to anagen [27]. However, human studies on latanoprost and bimatoprost have yielded mixed results, possibly due to varying doses and research methodologies [28]. Minimal effects were observed only when used in combination with corticosteroids [27, 29]. Compared to topical steroid therapy, prostaglandin analogs have not shown superior efficacy but are noted for their lower potential for side effects compared to steroids [30].

Minoxidil: Minoxidil is typically used as an adjunct treatment for other forms of alopecia areata therapy, often in an off-label manner. While the exact mechanism of action remains unclear, it is believed that minoxidil works by dilating blood vessels in the scalp, thereby improving blood flow. It promotes the transition from the telogen phase to the anagen phase by acting on potassium channels [31,32]. Minoxidil is available over the counter in various concentrations, typically 2–5%. Adverse effects that can occur during treatment include hypertrichosis, contact dermatitis, and irritation, the latter being more common with the foam version, which does not contain propylene glycol [31]. Minoxidil generally has a favorable safety profile, although a few cases of cardiovascular effects have been reported in the pediatric population [31,33,34]. Due to hypertrichosis, the 5% formulation is not recommended for women [35]. A commonly reported side effect of minoxidil therapy is temporary hair shedding, which typically occurs about a month after starting treatment. This

is caused by the stimulation of hair follicles in the telogen phase to re-enter the anagen phase, leading to the synchronization of the hair cycle in multiple follicles simultaneously. This is a temporary issue, as the hair cycle normalizes after a few weeks to months of continued therapy [31,33,34]. Since the discovery of minoxidil's ability to counteract hair loss, several studies have been conducted to evaluate its efficacy in alopecia areata. These studies have used concentrations of 1% and 2% in patients with mild disease and 3% in those with more severe alopecia areata. The findings suggest that minoxidil has beneficial effects in mild cases of alopecia areata, but its efficacy in more severe cases is less convincing [31]. Minoxidil is often used in combination with other topical agents or systemic therapies, as monotherapy has not shown significant improvements [13,35,36].

Contact Immunotherapy: The contact allergens used for immunotherapy in alopecia areata include squaric acid dibutyl ester (SADBE) and diphencyprone (DPCP). Both DPCP and SADBE are non-mutagenic and offer similar efficacy and relapse rates. A 2010 study demonstrated that DPCP achieves a response rate of 60% in severe cases of alopecia areata, 17% in cases of alopecia totalis or universalis, and between 88% and 100% in patients with patchy alopecia areata [37]. A more recent study from 2023 reported similar results with SADBE, with a total response efficacy of approximately 60% [38]. Regarding variations in treatment efficacy among different patient groups, it has been noted that patients under 16 years old with severe alopecia areata, as well as older patients, tend to have weaker responses to treatment. However, the 2023 study suggests that while these differences exist, they are not statistically significant. Prognosis is more strongly influenced by the duration of the disease and the severity of the initial episode [39]. Topical immunotherapy works through various mechanisms. One primary effect is the reduction of the CD4 to CD8 lymphocyte ratio from 4:1 to 1:1, along with a decrease in intrabulbar CD6 lymphocytes and Langerhans cells. Happle et al. introduced the concept of "antigenic competition," where an allergic reaction induces suppressor T cells that non-specifically inhibit autoimmune reactions against hair follicle components. Following topical immunotherapy, the expression of class I and II MHC molecules, which are typically elevated in alopecia areata-affected areas, returns to normal levels. Contact allergens help attract new T cells to the treated areas of the scalp, assisting in the clearance of potential follicular antigens. The "cytokine inhibitor" theory proposes that contact allergens may interfere with pro-inflammatory cytokines and their continued production by follicular keratinocytes [40]. Topical immunotherapy can cause side effects

such as persistent dermatitis, painful cervical lymphadenopathy, generalized eczema, blistering, contact leukoderma, and urticarial reactions [37].

Anthralin (Dithranol): Anthralin is a topical medication primarily used in the treatment of psoriasis in children due to its anti-mitotic effects. It works by generating free radicals and exhibits keratoplastic, keratolytic, bactericidal, fungicidal, and anti-seborrheic properties [41]. Its therapeutic effect is attributed to immunosuppressive and anti-inflammatory actions. It reduces levels of TNF-alpha and TNF-beta. In the treatment of alopecia areata (AA), anthralin was introduced in 1985 when it was observed to induce contact dermatitis, a beneficial side effect for stimulating hair regrowth. To be effective, anthralin must be administered in high concentrations (above 0.5%) [41,42,43]. Remarkable results have been observed at a concentration of 1%, particularly in the pediatric population, where 35.3% achieved complete hair regrowth, and 42.1% experienced partial regrowth [44]. Some studies also reported effectiveness with a 0.2% ointment in the pediatric population [45]. Anthralin has proven useful in patients with extensive alopecia areata, showing a response rate of about 62.5% [46]. A retrospective case series in 2015 involving patients with chronic, extensive, or treatment-resistant AA showed that anthralin combined with DPCP was significantly more effective than DPCP alone in contact immunotherapy, with 72% achieving complete hair regrowth, compared to the group using DPCP alone [47]. However, other studies have shown conflicting results, with some indicating that DPCP monotherapy was as effective, or even more effective, than the combination therapy [48,49,50]. It has been suggested that combining anthralin with DPCP should be considered in patients who do not respond to DPCP monotherapy [52]. A 2022 review summarized the effectiveness of topical immunotherapy with DPCP, SADBE, and anthralin. Anthralin was found to be the least effective, but its results were the most long-lasting [51]. The duration of therapy is an important factor, with longer treatment times (more than 8 months) leading to better outcomes.Additionally, there has been a reported case of a successful and effective combination of anthralin and calcipotriol. Further research is recommended to explore this combination [53].Side effects are common and include mild pruritus and erythema. Less common side effects, affecting about one-third of patients, include transient folliculitis and regional lymphadenopathy [46].

Topical Tacrolimus: Tacrolimus is a topical calcineurin inhibitor that works by blocking T-lymphocyte activity, thereby reducing IL-2 and IFN-gamma activity [54,55]. Initially, studies

using animal models suggested that tacrolimus could be a useful treatment for alopecia areata (AA). However, clinical trials on patients revealed that the drug did not contribute to significant hair regrowth. The primary issue was its limited penetration into the skin due to the large molecular weight of the drug and the intact epidermal barrier of the scalp [54,56,57]. Researchers have attempted to enhance drug penetration by using occlusion. Subsequent studies using 0.1% tacrolimus ointment achieved positive results, particularly in patients with a shorter disease duration or patchy alopecia, even without the use of occlusion [58,59,60]. While some improvement was observed, it was less significant compared to other topical treatments [61].

Systemic Treatment

Systemic Glucocorticosteroids: Systemic glucocorticoids are recommended for patients with a SALT score above 20. Commonly used systemic glucocorticoids include prednisone, betamethasone, methylprednisolone, and dexamethasone. This treatment method is known for its high efficacy but also for a high relapse rate. While patients often respond well and may achieve remission, relapse frequently occurs upon tapering or discontinuing the medication. However, studies have shown that relapse rates can be reduced by combining systemic glucocorticoids with minoxidil therapy [62]. Glucocorticoids can be administered continuously, either orally or intramuscularly, until remission is achieved (typically for 6 to 12 weeks), or in a pulsed fashion. There is no significant difference in efficacy between intravenous and oral administration routes. In pulse therapy, the medication is administered on two consecutive days per week over the course of several months, with oral or intravenous routes available [13]. Pulse therapy is generally preferred as it is associated with fewer side effects compared to daily steroid administration, although the continuous method is still an option. A large study conducted in 2022 found that pulse therapy is as effective as continuous therapy but with fewer side effects and a lower recurrence rate: "Median baseline SALT score was 65.3% (range 9.5–100). After 24 weeks of MPCT-OD, 88.9% (40/45) of the patients showed an improvement in SALT score with a median change in SALT of 71.1%. Of the patients who experienced an improvement in SALT score, 25% had complete hair regrowth (10/40)." [63] However, there is still no consensus on the optimal dosing or specific type of glucocorticoid to be used in pulse therapies. A 2023 study highlighted that betamethasone demonstrated the best efficacy but also had the highest rate of side effects. Pulse therapy can also be combined with intralesional steroids, other topical treatments (e.g., minoxidil), or

systemic therapies (e.g., methotrexate) for better outcomes [54]. Common side effects associated with systemic glucocorticoids stem from adrenal suppression, such as long-term effects on bone growth or integrity, ocular changes, and exacerbation of hypertension and/or diabetes. The longer steroids are used, the more severe and dangerous the side effects become. When used for less than six months, side effects such as weight gain and mood instability are commonly observed [62]. Despite the risks, systemic steroids remain popular among patients due to their affordability compared to more expensive treatments, such as JAK inhibitors [63].

Methotrexate (MTX): Recent studies suggest that methotrexate (MTX) may exert a disease-modifying effect by inhibiting the JAK/STAT pathway, which plays a critical role in inflammatory and immune responses [64]. MTX is used to treat alopecia areata (AA) resistant to conventional therapies, showing good tolerability and positive outcomes, particularly in the adult population. According to recent studies, satisfactory therapeutic outcomes have been achieved in 49.7% to 70% of cases [65,66,67]. The best results were observed in patients who received methotrexate in combination with corticosteroids. This co-therapy was well-tolerated, with side effects, such as transient liver dysfunction, occurring rarely and being manageable for most patients. The optimal treatment duration, according to studies, is approximately 28.1 weeks; however, prolonged therapy may be necessary to maintain therapeutic effects [66]. Guidelines recommend starting treatment at a dose of 5-10 mg per week, with a gradual increase to 20-25 mg per week. During methotrexate therapy, folic acid supplementation is essential, with a recommended dose of no less than 15 mg per week [13].

Cyclosporine: Cyclosporine is a calcineurin inhibitor and an immunosuppressive drug that primarily functions by inhibiting the synthesis of interleukins crucial for T-lymphocyte activation. Initially used in transplant medicine, cyclosporine has also found application in the treatment of severe alopecia areata (AA) (SALT score 50-94). It can be used as monotherapy or in combination with corticosteroids, most commonly methylprednisolone. According to recent studies, combination therapy with corticosteroids has proven more effective, achieving a 69% success rate compared to 57% with monotherapy. Additionally, the recurrence rate is lower in combination therapy (36%) compared to monotherapy (74%) [68,69]. Side effects were reported in 37% of patients during therapy, with the most common being gastrointestinal issues, hypertrichosis, and hypertension. The recommended dosage for cyclosporine is 5.1 mg/kg/day when used as monotherapy and 3.29 mg/kg/day when combined with corticosteroids [68,69].

Azathioprine: Corticosteroids are undoubtedly the first-line treatment for alopecia areata (AA); however, long-term use is discouraged due to the potential for undesirable systemic side effects. This creates a need for steroid-sparing immunosuppressive agents. Azathioprine works by inhibiting DNA synthesis, which suppresses T-cell proliferation and cytokine release, ultimately reducing the immune response against hair follicles. It can be used in cases of recurrent AA that have not responded to standard treatments. There are cases where azathioprine has been used in pediatric patients, with each receiving a dose of 1 mg/kg. Significant hair regrowth was observed within 4 to 8 weeks, and treatment was continued for 6 to 12 months to maintain remission. All patients showed sustained improvement, and the study reported no major side effects. Although azathioprine has shown promising results as an alternative to corticosteroid treatment, further investigation through large-scale, placebo-controlled studies is needed to confirm its efficacy and better understand its side effects [70].

JAK Inhibitors: JAK inhibitors represent a modern approach to treating alopecia areata (AA) by targeting the JAK/STAT pathway, a key mediator of inflammatory and immune responses in AA. Inflammatory molecules in AA are mediated by JAK kinases, making JAK inhibitors a promising systemic therapy. These small molecules work by competing with ATP for binding in the kinase domain, preventing JAKs from phosphorylating their substrates, thereby reducing the inflammatory reaction within the hair follicle. In the human body, different JAK kinases exist, including JAK1, JAK2, JAK3, and TYK2 [4,71]. JAK proteins are involved in the signaling pathways of various hormones, growth factors, and cytokines. Interfering with these pathways affects multiple physiological processes, leading to a range of adverse effects. The most common side effects include minor issues such as acne, headaches, nausea, urinary tract infections, respiratory tract infections, anemia, thrombocytopenia, neutropenia, and elevated creatinine levels. Serious side effects, such as pneumonia, sepsis, or non-melanoma skin cancer, are also possible but less frequent [4]. JAK inhibitors are classified into two generations: the first generation, which inhibits JAK kinases non-selectively, and the second generation, which selectively inhibits specific JAK kinases [4]. Second-generation JAK inhibitors are designed to target a single JAK isoform, potentially reducing the risk of side effects and improving therapy compliance. However, there are currently no official guidelines regarding the use of second-generation JAK inhibitors for AA, including recommendations for appropriate dosing and the management of side effects.

First-Generation JAK Inhibitors:

Ruxolitinib: A JAK1/JAK2 inhibitor, ruxolitinib exerts its therapeutic effects by inhibiting cytokine signaling (JAK1/JAK3) and IFNγ signaling (JAK1/JAK2). A 2014 study demonstrated significant therapeutic effects, with nearly complete hair regrowth in adults and children with moderate to severe AA [72]. However, hair loss often recurred after discontinuation of the treatment. Trials with topical ruxolitinib 1.5% cream showed outcomes comparable to placebo [73].

Tofacitinib: A JAK1/JAK3 inhibitor, tofacitinib works similarly to ruxolitinib and is used in patients with moderate to severe AA. Studies from 2016-2017 showed response rates of 64-77% in patients taking 5 mg twice daily, with 32-58% experiencing more than a 50% improvement in their SALT score [74]. However, relapse occurred in many patients shortly after discontinuation of the treatment. While there have been small studies in pediatric patients using topical tofacitinib, showing a 66% response rate, larger placebo-controlled studies are needed to validate these findings [4].

Baricitinib: A JAK1/JAK2 inhibitor, baricitinib first showed clinical promise in 2015 in a case involving a patient with multiple autoimmune diseases, including AA. After treatment with both topical and systemic baricitinib, the patient experienced complete hair regrowth, and immune markers associated with AA, such as MHC I and II expression and CD8+ T-cell infiltration, were significantly reduced [75]. These findings led to the BRAVA-AA1 and BRAVA-AA2 trials, involving over 1,200 patients. The trials showed that patients with severe AA who received oral baricitinib at 4 mg/day had a 35.9-38.8% success rate (measured as a SALT score ≤ 20) after 36 weeks [76].

Second-Generation JAK Inhibitors:

Abrocitinib: A JAK1-specific inhibitor, abrocitinib is primarily used in the treatment of atopic dermatitis (AD). While not routinely used for AA, there are positive indications of its efficacy. A clinical case report from 2022 described a patient with AD and AA who had failed to respond to previous treatments. After 12 weeks of treatment with 200 mg/day of abrocitinib, significant hair regrowth was observed, with no symptoms of AA after one year of treatment and no adverse side effects [77].

Brepocitinib: A JAK1/TYK2 inhibitor, brepocitinib was tested alongside ritlecitinib in the ALLEGRO trial. In the trial, 47 patients with severe AA received 60 mg of brepocitinib daily for 4 weeks, followed by a reduction to 30 mg for the next 20 weeks. After 24 weeks, 64% of

patients achieved a 30% reduction in their SALT score (SALT30). However, two patients dropped out of the study due to severe side effects [4,78].

Ritlecitinib: A JAK3/TEC family kinase inhibitor, ritlecitinib was also tested in the ALLEGRO trial. In this trial, 48 patients with severe AA received 200 mg of ritlecitinib daily for the first four weeks, followed by 50 mg daily for the next 20 weeks. After 24 weeks, 50% of patients achieved SALT30, compared to only 3% in the placebo group. Moreover, the side effects of ritlecitinib were comparable to those observed in the placebo group, suggesting it may be an effective and safe treatment option for patients with severe AA [4,78].

PDE-4 Inhibitors:Apremilast is an inhibitor of phosphodiesterase 4 (PDE4), a key enzyme in inflammatory cells. Phosphodiesterase (PDE) enzymes catalyze the conversion of cyclic AMP (cAMP) to AMP, thereby upregulating inflammatory pathways [79]. By inhibiting this enzyme, apremilast decreases cAMP levels, leading to a reduction in inflammatory responses. Specifically, it decreases the expression of TNF-alpha, IL-23, and IL-17, while increasing the production of the anti-inflammatory cytokine IL-10 [80]. In a 2015 study, AA-like hair loss was induced in mice, and apremilast was administered before the disease could develop. The results indicated that apremilast might have a preventative effect in AA, as the control group developed AA-like hair loss, while the treated mice did not [81]. Additionally, a case study involving a patient with both psoriasis and ophiasis-type AA, who had not responded to traditional treatments, showed that after taking apremilast, both conditions went into remission, and scalp hair regrowth occurred within six weeks. However, gastrointestinal side effects from oral apremilast, such as severe discomfort, were significant enough to threaten treatment discontinuation [82]. Crisaborole, a topical PDE4 inhibitor, may offer a solution to the gastrointestinal side effects associated with oral apremilast. One case study reported that a patient with patchy AA experienced rapid improvement with crisaborole, achieving 40% hair regrowth within one month [83]. In 2018, a larger study tempered expectations regarding PDE4 inhibitors. In a double-blind, placebo-controlled trial, no statistically significant difference was found between the apremilast group and the placebo group. In fact, the mean percentage improvement in the SALT score was higher in the placebo group (9.01%) compared to the apremilast group (1.45%) [84]. Researchers from India suggested that the lack of efficacy in the 2018 study might have been due to the short duration of treatment and the severity of the AA cases included. In their study, 15 patients with mild to moderate AA, who had not responded to traditional treatments, experienced disease stabilization and hair

regrowth with apremilast, with 60% showing a 50-74% improvement. This assessment was based on patient self-evaluations using a 1-10 scale and physician global assessment, comparing photographs taken before and during treatment. However, relapse occurred after approximately two months, and the patients were concurrently using treatments such as oral corticosteroids [85].

Biological Treatment:

Dupilumab: The use of dupilumab in the treatment of alopecia areata (AA) remains a controversial topic. It is a fully human monoclonal antibody produced in Chinese hamster ovary cells via recombinant DNA technology. Dupilumab works by binding to the alpha subunit of the interleukin-4 (IL-4) receptor, thereby blocking signaling mediated by IL-4 and IL-13 [86]. This action leads to the downregulation of the Th2 immune response, which plays a role in the pathogenesis of both atopic dermatitis (AD) and AA [87]. Initially developed for treating atopic dermatitis, dupilumab has shown promise in treating AA. In 2018, a study reported that patients with both AD and AA showed clinical improvements in both conditions after dupilumab treatment [88]. A subsequent 2020 study focused primarily on dupilumab's effects on AA (in patients with coexisting AD) and found a reduction in SALT scores, indicating hair regrowth. It was also found that patients with high levels of Th2-related chemokines (TARC) responded well to dupilumab, while those with low TARC levels, indicative of a Th1-dominant immune response, did not respond as effectively [89]. It has been proposed that downregulation of Th2 may lead to increased activity of Treg lymphocytes, which play a critical role in maintaining hair follicle health [87]. Larger clinical studies have supported this hypothesis, showing that a subset of AA patients with serum IgE levels ≥200 IU/mL responded better to dupilumab treatment than those with <200 IU/mL, making it a potential option for patients with high IgE levels [90]. However, some patients with coexisting AD and AA experienced worsening of AA after dupilumab treatment. Although the exact mechanism is unknown, it has been suggested that this may be due to a psoriatic-like reaction caused by an imbalance in lymphocyte populations, particularly Th2 and Th1/Th17, and an increase in interferon-gamma [91]. Dupilumab may exacerbate AA in patients with a short history of both AA and AD, especially if no other atopic comorbidities are present, possibly by enhancing the Th1 response [87]. A 2022 case study described a patient with alopecia totalis who benefited from long-term dupilumab therapy, combined with topical corticosteroids, resulting in sustained hair regrowth over three years without relapse [92]. A

2024 review highlights dupilumab's potential as a therapeutic option for patients with atopic comorbidities who are at risk for tuberculosis and should avoid JAK inhibitors. Dupilumab is generally safe, with rhinitis and conjunctivitis being the most commonly reported side effects [92].

Ustekinumab: Ustekinumab is a fully human IgG1k monoclonal antibody produced using recombinant DNA technology in a mouse myeloma cell line. It binds to the p40 protein subunit of IL-12 and IL-23 cytokines, inhibiting their activity and preventing these cytokines from binding to their receptors. IL-12 and IL-23 are implicated in autoimmune diseases such as psoriasis and psoriatic arthritis [93]. In AA, IL-23 activates Th17 lymphocytes, which are involved in the inflammatory response. Elevated levels of Th2, IL-23p19, IL-23/IL-12p40, and cytokines produced by Th17 (IL-6, IL-17, IL-22, TNF-α) are observed in AA patients [94]. In early trials, ustekinumab showed promise in treating AA. In one case, a patient with alopecia universalis experienced complete regrowth of body hair and 85% of scalp hair by week 20, with full scalp regrowth by week 49. Gene expression analysis revealed suppression of inflammatory markers, particularly Th2-related genes, and increased expression of hair keratins post-treatment [95]. However, a 2018 study suggested that blocking IL-12 function may be more critical for AA improvement. A small clinical trial involving pediatric patients with AA showed mixed results in hair regrowth [96]. Ustekinumab could be a viable option for patients who do not respond to conventional therapy. While mild side effects such as headaches and sinusitis are common, there is a risk of serious infections with its use [97].

Abatacept: Abatacept is a fusion protein consisting of the CTLA-4 fragment and human IgG1, produced via recombinant DNA technology in Chinese hamster ovary cells. As a CTLA4-immunoglobulin costimulatory modulator, it reduces inflammatory responses by inhibiting immune cell activation signals [97]. Genetic studies of AA patients have shown a strong genetic susceptibility at the CTLA4 locus. An open-label, single-arm clinical trial with 15 patients demonstrated varying degrees of hair regrowth in 9 patients. One patient showed significant regrowth, with over 50% hair restoration, while others experienced intermediate to minimal regrowth [98]. The trial suggested that abatacept might be more effective when combined with other treatments, such as JAK inhibitors, though larger studies are needed [98]. Potential side effects of abatacept include headaches and infections [99].

Others:

Platelet-Rich Plasma (PRP): Platelet-rich plasma (PRP) was first introduced in 1990 as a hemostatic agent for non-healing wounds. Since then, it has gained popularity in various medical fields, including dermatology. PRP's effectiveness in stimulating hair regrowth is attributed to the presence of over 20 growth factors that activate specific pathways, promote the anagen phase of hair growth, and inhibit apoptosis. Additionally, PRP plays a role in processes such as angiogenesis, wound repair, and cell proliferation [100]. Several small trials have investigated PRP's effect on alopecia areata (AA), with reported success rates ranging from 52.8% to 70%, depending on the study, the stage of AA, and the PRP dosage. One of the most notable results came from a 2017 study that compared PRP with minoxidil. In this study, 90 patients were enrolled, with 30 patients receiving PRP at a dose of 4 ml every four weeks. After three sessions of PRP (12 weeks), 70% of the patients experienced significant hair regrowth. The treatment was found to be safe, with only minor side effects such as mild headaches, temporary pain, itching, or transient erythema reported [101]. While the evidence suggests that PRP could be an effective and safe treatment for patients with AA, there is a lack of standardized protocols, and further large-scale research is necessary to fully assess its therapeutic potential [100,102].

Phototherapy: The primary principle of phototherapy is to induce apoptosis in T cells, thereby interrupting autoimmune activity and promoting hair regrowth. Phototherapy is typically used for AA patients who have not responded to traditional treatments. Narrowband Ultraviolet B (NBUVB) phototherapy has shown mixed results in treating AA, while some patients have experienced excellent hair regrowth, the majority have shown poor results [103]. Topical PUVA therapy, which combines psoralen (8-methoxypsoralen) with UVA light, has demonstrated better results. In one study 105 out of 149 patients showed good to excellent hair regrowth after PUVA treatment, with only mild side effects such as erythema or a burning sensation [103]. UVA-1 phototherapy, which uses light with wavelengths of 340-400 nm, has been shown to result in improvements ranging from 30% to 60%. The side effects associated with this therapy are mild, including hyperpigmentation and skin dryness [103]. In 2020, a study explored the use of 308-nm excimer lamp therapy for AA. Four patients with at least one large patch or two separate patches of hair loss underwent weekly sessions of irradiation, starting at 150 mJ/cm^2 and increasing until mild erythema was observed. Over 12 weeks, significant hair regrowth was noted in the treated patches compared to control areas. Additionally, no hair loss was observed during follow-up, and there were fewer signs of active AA. Although this study is promising, larger-scale studies are needed to confirm the results

[104]. While various types of phototherapy, including NBUVB, PUVA, and UVA-1, have shown potential in treating AA, many of the studies have small sample sizes. Moreover, despite the minimal side effects observed, there is a recognized risk of photocarcinogenesis (skin cancer development) with prolonged or repeated exposure to phototherapy [105]. Therefore, while phototherapy remains an option for treating AA, further research is necessary to fully establish its efficacy and safety.

Discussion :

The treatment of Alopecia Areata (AA) presents significant challenges for clinicians. Current research suggests that treatment protocols recommend topical medications as first-line therapies for patients with low SALT scores. Topical corticosteroids have been confirmed to be effective in this patient population, with various application methods available. However, the deeper the method of application, the higher the risk of systemic side effects. Conversely, there are strategies to minimize the systemic impact of steroids. Given that patient responses are highly individualized, research suggests that intralesional corticosteroid administration is more effective than topical applications. Other agents, such as anthralin, minoxidil, crisaborole, and topical tacrolimus, are less potent than glucocorticosteroids but have a more favorable side effect profile. These agents are considered useful as part of combination therapy with other topical or systemic drugs, as the additive effect may improve the likelihood of hair regrowth. Topical treatments are available in various forms, including ointments, gels, foams, and intralesional injections. When selecting a treatment method, clinicians must consider patient adherence and their ability to administer the treatment correctly. Many researchers have indicated that poor outcomes in topical treatment are often due to the short duration of therapy. Therefore, longer treatment plans are preferred. Prostaglandin analogs, however, appear to be the least effective option. Contact allergen therapy is another topical choice, often used in more advanced stages of AA. However, the longer the duration of hair loss, the lower the likelihood of a positive outcome. This treatment can also be inconvenient for patients due to the localized dermatitis it may cause. For patients experiencing hair loss over a large area of the scalp, systemic therapy is recommended. These medications are predominantly immunosuppressive, leading to risks of infection and other serious side effects. Systemic steroids are now commonly administered as pulse therapy to reduce immune suppression, offering similar efficacy to daily dosing. Azathioprine and cyclosporine are other immunosuppressive drugs that specifically target certain immune pathways, making them less

likely to affect the entire immune system compared to steroids. However, due to a lack of large-scale clinical trials, these drugs are considered second-line treatments. Cyclosporine may also be used to enhance the effects of steroids. PDE-4 inhibitors are not recommended for oral use due to their gastrointestinal side effects. JAK inhibitors represent a promising therapeutic option for patients who have not responded to standard therapies. However, as this is a relatively new treatment approach, formal guidelines have not yet been established. Despite the potential of JAK inhibitors, relapse rates remain high. Dupilumab is another option for patients at high risk for tuberculosis who cannot use JAK inhibitors. Its efficacy is comparable to JAK inhibitors, but it is particularly effective in patients with elevated IgE levels. Its effects can also be enhanced by combining it with topical corticosteroids. To further boost the effects of JAK inhibitors, abatacept may be added to the treatment regimen, although there have been few trials investigating this modification. Ustekinumab, another biological agent, may be considered for patients who do not respond to other treatments. For those who do not achieve satisfactory results with conventional treatments, phototherapy may be an option. While initial findings suggest some efficacy, large-scale trials are lacking, and frequent use of phototherapy has been associated with an increased risk of carcinogenesis. Similarly, small clinical trials suggest that platelet-rich plasma therapy may promote hair regrowth, though more research is needed. In summary, current research on AA treatment is increasingly focused on personalized therapies. These approaches not only improve treatment outcomes but also reduce the risk of adverse effects.

Conclusion :

Alopecia areata is an autoimmune disease that can be treated with drugs targeting different immune system reactions. To date, many patients are not satisfied with the results, or they do not achieve hair regrowth at all. They must wait for the outcomes of medications for extended periods, while also suffering from various side effects. Despite the disease being known for ages, patients' needs remain unmet. Treatment protocols around the world differ from one another, suggesting that there is no strong evidence favoring a single approach.It is important to approach each patient individually and select a therapy best suited to their disease stage, comorbidities, and overall health status. Additionally, it is crucial to start treatment as early as possible to halt the disease in its initial stages. Treatment should begin with topical therapies, but as the disease progresses, newer drugs should be introduced and combined with other methods to achieve even better outcomes. The results indicate that there are almost limitless

combinations and options for treatment, though patients often have to wait weeks to months for results. There is still a need to explore more drugs that directly target the immune reactions involved in the pathogenesis of alopecia areata. Furthermore, standardized treatment regimens for new medications and large-scale clinical trials are required to provide evidence of the efficacy of combined therapies.

Disclosure:

Author's contribution:

Conceptualization: JW

Methodology:KWP; JW

Software:KWP; MC,

Check: AU,WMS and MC;

Formal analysis: MK, KJ, MC, and KWP, JW

Investigation: JW; KWP

Resources: JW;

Data curation:MC, MP and AU

Writing-rough preparation: JW

Writing-review and editing: MJ, KWP, MP, and JP

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