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Review

CYTOKINE-TARGETED TREATMENT IN ALOPECIA AREATA - NEW POSSIBILITIES?

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ABSTRACT

Alopecia areata is a form of non-scarring hair loss characterised by a recurrent and difficult-to-treat course. The aetiology of this disease is still incompletely understood. However, multiple immunological pathways and an abnormal cytokine profile in patients with alopecia areata have been described. There are many therapeutic options for patients with alopecia areata, including topical, intralesional or systemic corticosteroids, contact immunotherapy, phototherapy and non-corticosteroid immunosuppressive drugs such as cyclosporine, methotrexate or azathioprine. However, these treatments have limited efficacy and may be associated with side effects. In addition, Janus kinase inhibitors have been shown to cause metabolic disorders. Therefore, their use in patients with alopecia areata may be limited. Other cytokine-targeted therapies have been shown to be effective in alopecia areata, such as apremilast (a phosphodiesterase 4 inhibitor), ustekinumab (a human immunoglobulin (Ig) G1 kappa monoclonal antibody directed against interleukin 12 and 23), abatacept (a soluble fusion protein which links the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 to the modified Fc portion of human immunoglobulin G1), secukinumab (an IL-17A antagonist) and dupilumab (a monoclonal antibody that blocks interleukin 4 and interleukin 13). TNF inhibitors (such as infliximab, adalimumab and etanercept) have been described to be ineffective in alopecia areata. In addition, disease exacerbation after TNF therapy has been reported. Alefacept (an immunosuppressive dimeric fusion protein that consists of the extracellular CD2-binding part of human leukocyte function antigen-3 fused to the Fc part of human IgG1) and efalizumab (anti-CD11a monoclonal antibody) have not shown efficacy in alopecia areata. There are also isolated reports of alopecia areata after therapy with omalizumab (recombinant humanised monoclonal antibody anti-IgE), ixekizumab (inhibitor of IL-17A) and brodalumab (inhibitor of IL-17R).

KEYWORDS: alopecia areata, cytokines, treatment.

1. Introduction

Alopecia areata is a dermatological autoimmune disease characterised by non-scarring hair loss. This loss is unpredictable and often characterised by a variable evolution. It does not affect only the scalp and can take the form of both well-demarcated hairless areas and diffuse or total alopecia, when all hair sites are affected [1]. It is a disease whose aetiology has not been fully elucidated, with causes attributed to environmental, genetic and immunological factors. Therefore, one of the directions that dermatology is currently focusing on is the use of appropriate targeted therapies for the particular immune pathways that appear to be of heightened activity in this particular disease [2]. Appropriate treatment is very significant because alopecia areata has a huge impact on the patient's psyche [3], often leading to mood disorders, anxiety and low self-esteem [4].

2. Patophysiology

In order to administer an appropriate therapy for alopecia areata, an understanding of the aetiology of this disease is needed. What needs to be emphasised is that the immune activation that takes place in this dermatological disease is still not completely understood [5]. One of the more commonly described theories is the breakdown of the immune privilege system, which may be the cause of autoimmune diseases. A prerequisite for the proper progression of the hair cycle is the appropriate interdependence occurring between the hair follicle and its immunological microenvironment. Some elements of the hair follicle, including the bulge (during the entire hair cycle) and the bulb (during the anagen phase), retain relative immune privilege. When this privilege is disrupted, an immune attack is triggered by inflammatory infiltrates, resulting in alopecia [6]. Genetic and other

predispositions coupled with initiating stimuli (e.g. viral infection) lead to loss of hair follicle immune privilege (HF-IP) due to a local increase in IFN-γ levels and induce an autoimmune response targeting exposed hair follicle autoantigens via activation of autoreactive CD8+NKG2D+ cytotoxic T cells [7]. A number of cytokines have also been identified in the pathogenesis of alopecia areata, whose levels are abnormal in this dermatological condition, e.g. IL-4, IL-10, IL-13, IL-15, TGF-ß1, α-MSH, PDE 4, CCL-18 etc. [7, 8]. Alopecia areata has been shown to be associated with other dermatological and autoimmune diseases such as atopic dermatitis, psoriasis, thyroid diseases, lupus erythematosus and vitiligo [9]. Cells and pro-inflammatory factors only act on hair in the anagen phase, causing it to enter the catagen phase too early [10]. Due to the inflammation-induced dystrophy, the hair follicle is no longer able to hold the hair shaft in the canal and this results in hair loss. What is significant is that, unlike in scarring alopecia, the hair follicle stem cells are not destroyed and have a preserved regenerative capacity [11].

3. Treatment

Despite numerous studies, it has still not been possible to invent a therapy that is completely effective and free of any side effects, especially in extensive alopecia areata [5]. The drugs used, such as topical and systemic corticosteroids, tacrolimus, anthralin or cyclosporine, for example, often cause numerous side effects and their efficacy is only temporary due to the chronic nature of the disease [12]. Therefore, also due to the prevalence of the disease [13] and the need to help many people worldwide, more and more research is being conducted into new treatments that target specific molecular mechanisms underlying the pathophysiology of alopecia areata [8,14]. One of the new treatments used in alopecia areata is therapy aimed at inhibiting Janus kinases (e.g. tofacitinib, ruxolitinib), due to increased expression of the JAK-STAT signalling pathway, which has been shown to be one of the key factors involved in the initiation and progression of alopecia areata [15]. Although oral JAK inhibitors appear to be effective in the treatment of alopecia areata, their systemic use may be associated with long-term side effects. Possible side effects include hypercholesterolaemia, neutropenia, thrombocytopaenia, increased serum creatinine, and viral, mycobacterial as well as fungal infections [16]. Therefore, the efficacy and effect profile of other cytokine-targeted therapies in alopecia areata will be addressed in the following section.

4. Emerging treatments

4.1. PDE 4 Inhibitors

They act by decreasing phosphodiesterase type 4 activity, which is associated with an increase in cAMP levels in inflammatory cells, which in turn results in a decrease in the release of pro-inflammatory mediators and cytokines [17]. PDE 4 inhibitors are registered for the treatment of psoriatic arthritis, atopic dermatitis and inflammatory airway diseases, among others [17]. The literature reports that PDE 4 levels are increased in alopecia areata and therefore these are drugs that are being researched and hoped for. In one study in a humanised mouse model using human scalp grafts, after creating molecular conditions as in alopecia areata, apremilast (no information on dosage is available) applied for 31 days showed high clinical and molecular efficacy, as a therapeutic effect in 11 of 13 grafts was seen in the form of almost complete hair preservation and a reduction in IFN-γ and TNF-α levels. In contrast, in the control group in which apremilast was not used, 12 of 14 human scalp transplants showed an expected hair loss similar to that in alopecia areata [18]. However, it is worth noting that in another study, nine patients with severe alopecia areata (at least 50% scalp hair loss) were treated with apremilast 30 mg orally twice daily for 3-6 months, in whom no other therapy had previously worked. No scalp hair regrowth was reported in any of the patients who took part in the study [19]. In a double-blind, placebo-controlled pilot study in 30 patients with moderate-to-severe AA, the use of apremilast at the same dose as in the previous study showed no benefit over placebo [20]. The two studies that failed to demonstrate the efficacy of apremiliast were conducted in patients with moderate to severe alopecia areata, so future studies may be needed to investigate the efficacy of this drug in alopecia areata of mild severity. It is worth mentioning that cases have been described in the literature where treatment of alopecia areata with apremilast for a period of 6 weeks to 6 months at a dose of 30 mg once or twice a day has resulted in visible treatment effects [21-25]. Apremilast is relatively well tolerated by patients and requires little monitoring, while the most commonly reported side effects of this drug include diarrhoea, nausea, headache and emesis [26].

4.2. Abatacept

Composed of a fragment of human lymphocyte-associated antigen 4 (CTLA-4) and a fragment of human immunoglobulin IgG1, this drug is currently approved for the treatment of rheumatoid arthritis, among others [27]. Abatacept results in decreased T-lymphocyte proliferation by affecting the blockade of the costimulatory interaction with APC cells, which is necessary for lymphocyte activation. In addition, it leads to a reduction in levels of important inflammatory mediators, which include IFN-γ and IL-2 [28]. In alopecia areata, activated T lymphocytes play a very important role in the pathophysiology, which is why there are studies on the efficacy of abatacept in the treatment of alopecia areata. In one study, 15 patients with moderate to severe alopecia areata were administered 125 mg of abatacept subcutaneously every day for 24 weeks. One subject experienced significant hair regrowth and the treatment achieved the primary endpoint of >50% hair regrowth from baseline. It should be noted that the response was sustained after cessation of treatment and hair regrowth was maintained at post-treatment follow-up visits even at week 36. Four patients had intermediate hair regrowth (15-25%), four had low but noticeable hair regrowth (3-10%), and one patient had no hair regrowth on the scalp but on the eyebrows. In another four, treatment had no effect [29]. Abatacept is generally a well-tolerated drug and side effects that it may cause include headaches and infections [30], but in the study of Mackay-Wiggan et al. [29], side effects did not occur.

4.3. Dupilumab

Dupilumab, a human monoclonal antibody directed against the subunit α of the IL-4 receptor, leads to inhibition of signal transduction by IL-4, as well as IL-13, and consequently to inhibition of Th2 lymphocyte activation [31]. It is a drug showing great efficacy in the treatment of atopic dermatitis [32], and because of the association between this disease and alopecia areata, due in part to the activation of Th2 lymphocytes in both conditions, the possible efficacy of dupilumab in the treatment of alopecia areata is indicated [5]. There are a number of case reports where patients with concurrent atopic dermatitis and alopecia areata received a saturating dose of dupilumab of 600 mg, followed by subcutaneous injections every 2 weeks at a dose of 300 mg. The visible effect of the treatment in patients in the form of hair regrowth was seen after a period of several days to several weeks or months [33-42]. In another case report of a patient suffering simultaneously from atopic dermatitis and alopecia areata, treatment was started at a dose of 200 mg subcutaneously every two weeks. Already two weeks after starting therapy, the family reported hair regrowth in the patient [43]. Importantly, a randomised phase 2a clinical trial of dupilumab in patients with alopecia areata was also conducted. 20 patients received placebo, while 40 patients received dupilumab at a dose of 300 mg subcutaneously every week for 24 weeks. In these patients, there was significant hair regrowth compared to those who received placebo. After 24 weeks, both placebo and dupilumab patients were started on a weekly dose of 300 mg of dupilumab, which continued until week 48. Further hair growth was seen in a significant proportion of patients after dupilumab treatment [44]. However, it should be mentioned that, paradoxically, the occurrence of alopecia areata with new onset or its reactivation after dupilumab treatment was also reported. The timing of the appearance of alopecia areata symptoms after dupilumab administration, in the form of hair loss, varies widely. From 48 hours after the first injection of 600 mg of dupilimab [45] to as long as several days or several weeks after treatment [46-48]. The most common side effects of dupilumab include conjunctivitis, blepharitis or keratitis, as well as ocular pruritus or oral herpes [49].

4.4. Ustekinumab

Ustekinumab, which is a monoclonal antibody that inhibits the activity of cytokines IL-12 and IL-23 by binding to their common protein subunit p40 [50], has applications mainly in the treatment of psoriasis and Crohn's disease [51]. However, there are studies in which ustekinumab also has a positive effect in the treatment of alopecia areata. In three adult patients, whose course of the disease was characterised by extensive lesions, it contributed to an impressive improvement in hair growth. They were assessed for hair regrowth at 20 weeks after treatment with three subcutaneous doses of 90 mg ustekinumab given at weeks 0, 4 and 16. All three patients treated with ustekinumab showed varying degrees of hair regrowth after 20 weeks, with no reported adverse events during or after treatment [52]. A positive effect of ustekinumab treatment for alopecia areata has also been reported in children, as demonstrated by three clinical cases. In one patient, ustekinumab was administered subcutaneously at a dose of 90 mg at months 0, 3 and 6. The patient already showed significant hair regrowth three months after starting ustekinumab. The second and third patients were given a single 90 mg dose of ustekinumab subcutaneously and already after four months, the first patient showed complete hair regrowth, while the second patient's hair regrowth was partial, albeit visible [53]. It is worth mentioning, however, that another study conducted in the same year showed a lack of positive response, in four alopecia areata patients, to treatment with this human monoclonal antibody. The drug was administered subcutaneously in different doses and at different intervals. The first patient received 45 mg at month 0, 60 mg at month 1 and 90 mg at months 3 and 5. The second patient received 90 mg every 8 weeks for 30 months, while the third and fourth patients received 90 mg at months 0, 1, 3. None of them showed hair regrowth [54]. Furthermore, some studies have raised the possibility of ustekinumab inducing alopecia areata as a side effect of treatment with this drug. All cases reported in the literature concern patients with plaque psoriasis who were treated with ustekinumab at a dose of 45 mg subcutaneously, administered at different intervals, i.e. at 0, 4 and 16 week, or at 0, 4 and then every 12 weeks, at three-month intervals or in two doses with a one-month break. In each of these cases, patients noticed patches of hairless skin that had not previously occurred in them [55-57]. Ustekinumab is a relatively well-tolerated drug and reported adverse reactions following the drug include headaches, upper respiratory tract infections and allergic reactions at the injection site [58].

4.5. Tralokinumab

This human monoclonal antibody, which binds specifically to the cytokine IL-13 and leads to a decrease in its levels, is currently used successfully in the treatment of atopic dermatitis (AD) [59]. Due to the inhibition of the Th2 lymphocyte axis by tralokinumab, there are hopes for therapy with it in alopecia areata. In January 2020, the results of a randomised, double-blind, placebo-controlled pilot study (NCT02684097) involving a total of 22 people with moderate to severe alopecia areata were published. In the group, which received subcutaneous tralokinumab every 2 weeks for 24 weeks (no information on the dose is available), there were 15 participants at the start of the study, while only 2 completed the study. In the placebo group, 7 started the study, while only 1 participant completed the study, so the results cannot be considered authoritative [60]. Large randomised placebo-controlled clinical trials are needed to prove the effect of tralokinumab in the treatment of alopecia areata. Tralokinumab is a relatively well-tolerated drug and has mild to moderate adverse effects in patients treated for AD. The most common ones include those such as upper respiratory tract infection or headaches [61].

4.6. Secukinumab

Secukinumab, which is an IL-17A antagonist, is used to inhibit the inflammation found in plaque psoriasis, psoriatic arthritis and ankylosing spondylitis [62]. One reason for the development of alopecia areata is also believed to be an increase in IL-17A levels, and therefore the efficacy of secukinumab in the treatment of this disease is being investigated. To assess the efficacy and safety of this drug, a randomised double-blind study was conducted (seven patients received secukinumab and four

Table 1. Promising treatment options for alopecia areata targeting cytokines.

Author	Year	Agent	Duration of treatment	Number of patients	Treatment results	Adverse reactions
Liu et al.	2017	apremilast	3-6 months	N = 9	no scalp hair regrowth	diarrhea, nausea, headaches, and lethargy
Mikhaylov et al.	2019	apremilast	3-6 months	N = 10 (placebo) N = 20 (apremilast)	no benefit over placebo	nausea, diffuse arthralgia, and diarrhea
Magdaleno-Tapial et al.	2019	apremilast	15 weeks	N = 1	improvement	no information
Lopez et al.	2017	apremilast	6 months	N = 1	improvement	gastrointestial
Taneja et al.	2019	apremilast	4-17 months	N = 15	good or moderate response in 87% of patients	nausea, vomiting, and diarrhea
Estébanez et al.	2019	apremilast	6-12 weeks	N = 4	improvement	mild diarrhea
Sakakibara et al.	2019	apremilast	14 weeks	N =1	improvement	diarrhea and nausea
Mackay-Wiggan et al.	2021	abatacept	24 weeks	N=15	noticeable improvement in several patients	no adverse events
Kulkarni et al.	2022	dupilumab	injections every 2 weeks for 3 years	N = 1	almost complete regrowth of scalp hair after 8 months, no relapse after 3 years of use	no information
Aszodi et al.	2019	dupilumab	injections every 2 weeks for 11 months	N = 1	visible hair regrowth after 5 months of treatment, almost complete hair regrowth after 11 months	no adverse events
Ludriksone et al.	2019	dupilumab	injections every 2 weeks for 21-22 weeks	N = 2	total hair regrowth	no information
Patruno et al.	2019	dupilumab	injections every 2 weeks for 8-16 weeks	N = 2	significant hair regrowth	no adverse events
Uchida et al.	2019	dupilumab	6 months to 1 year	N = 7	significant hair regrowth in 6 out of 7 patients	no information
Magdaleno-Tapial et al.	2020	dupilumab	3 months	N = 1	significant improvement	no information
Smogorzewski et al.	2019	dupilumab	12 months	N =1	full, thick regrowth of terminal hairs on entire scalp after one year	no significant side effects
Darrigade et al.	2018	dupilumab	6 months	N = 1	full regrowth at month 6	slight conjunctivitis
Alniemi et al.	2019	dupilumab	8 months	N = 1	full regrowth of hair on scalp and eyebrows	no information
Sevray et al.	2019	dupilumab	8 weeks	N = 1	remarkable hair regrowth	no information
Gruenstein et al.	2020	dupilumab	4 months	N = 1	scalp hair has fully regrown	no information
Guttman-Yassky et al.	2022	dupilumab	48 weeks (first 24 weeks placebo or dupilumab, next 24 weeks all dupilumab). Then a follow-up visit every 4 weeks until week 72	N = 20 (placebo) N = 42 (dupilumab)	noticeably superior effect to placebo	mild upper-respiratory tract infection and mild-to-moderate conjunctivitis
Guttman-Yassky et al.	2016	ustekinumab	20 weeks	N =3	remarkable improvement	no reported adverse events
Aleisa et al.	2019	ustekinumab	a single injection or three injections at months 0, 3 and 6	N = 3	noticeable hair regrowth	no information
Ortolan et al.	2019	ustekinumab	3-30 months	N = 4	no hair regrowth	no information

Guttman	2020	tralokinumab	24 weeks	N = 15, only 2 completed the study (tralokinimab) N = 7 only 1 completed the study (placebo)	no reliable results	upper respiratory infection, injecton site reaction
Guttman-Yassky et al.	2019	secukinumab	20 weeks	N = 7 (secukinumab) N = 4 (placebo)	none of the patients who received secukinumab or placebo achieved SALT50	Plaque psoriasis exacerbation

placebo). Patients in the drug-treated group received 300 mg of secukinumab subcutaneously at weeks 0, 1, 2, 3 and 4, and every four weeks thereafter until week 20 of the study. The primary endpoint of the study was that patients achieved SALT50 (regrowth of at least 50% hair) at week 24 of the study. 8 out of 11 patients withdrew from the study for various reasons (lack of efficacy, no reason given for withdrawal, etc.). None of the patients who received secukinumab or placebo achieved SALT50. In the secukinumab-treated group, there was a slight hair gain in one patient, a slight loss in another, and no change in the remaining patients over the course of the study. Due to the low statistical power of this study, future studies may be required to confirm these findings, in which, for example, the dose of secukinumab will be higher, the dosing more frequent and the duration of the study longer [63]. It should be noted that there is also a case report in the literature of a psoriasis patient treated with 300mg of secukinumab subcutaneously at the same intervals as in the previous study, who developed alopecia areata [64]. Like any drug, secukinumab has some side effects. In this case, the most common include nasopharyngitis, upper respiratory tract infection and diarrhoea [65].

5. Ineffective drugs in alopecia areata and drugs after which alopecia may occur

Drugs that have been shown to be ineffective in alopecia areata include TNF-α inhibitors, which include infliximab, adalimumab and etanercept. In one multicentre study in France, in which these drugs were administered, French participating physicians were asked to report every time alopecia areata developed in patients taking this therapy. Some patients developed symptoms of alopecia areata, but the negative effect of the drugs cannot be clearly attributed to this issue, as the study group was small and some patients had a history of other autoimmune diseases [66]. One can also cite the case of a patient suffering from rheumatoid arthritis who, after subcutaneous injections of etanercept once every fortnight for the first 3 months and then once a month for the following 3 months, developed alopecia areata after 6 months of treatment, followed by alopecia universalis [67]. Alefacept, which inhibits the CD2 protein, has also been part of research into effective treatments for alopecia areata. In one randomised, double-blind study, patients with chronic and severe forms of this disease who were enrolled in the trial, taking 15 mg of alefacept weekly for 12 weeks, showed no statistically significant improvement compared to those who took placebo [68]. Another drug that was considered was efalizumab, an antibody directed against CD11a, but in this case it was also shown to be ineffective. In patients presenting with a moderate to severe disease picture, the efficacy of efalizumab therapy at a dose of 1.0 mg/kg every week for 12 weeks compared to patients taking placebo was not proven [69]. A case of alopecia areata after treatment of urticaria with omalizumab (an antibody that binds to human immunoglobulin E) at a dose of 300 mg once a month for 6 months subcutaneously also appeared in the literature. The first symptoms occurred 14 weeks after starting treatment, with the patient noticing hairless areas on his scalp [70]. Also after treatment of psoriatic arthritis with ixekizumab, which inhibits interleukin 17A, the onset of alopecia areata symptoms was reported 13 months after starting treatment (no dose given in the case report). Three months after discontinuation of the drug, scalp hair regrowth occurred [71]. Also after administration of brodalumab (no dose given in the case report), an IL-17 receptor antagonist, a psoriatic patient developed changes characteristic of alopecia areata 2 months after treatment [72]. It should be noted, however, that these are, for the time being, isolated case reports and further studies on the effects of these substances on alopecia areata must be awaited.

6. Summary

Treatment of alopecia areata is still unsatisfactory for both patients and doctors. New forms of treatment are being researched all the time, which may, in the future, improve the quality of life of patients struggling with this chronic inflammatory disease. Understanding the immunological pathways involved in the pathogenesis of alopecia areata and introducing safer and more targeted therapies is one of the goals of modern dermatology.

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