New Modalities in the Treatment of Refractory Alopecia Areata

Arzu Kılıç

Abstract

Alopecia areata (AA) is a common and complex T-cell–mediated inflammatory disorder. It may be patchy (localized), involve the entire scalp (alopecia totalis) or entire body (alopecia universalis). Alopecia totalis and universalis are often difficult to treat. Although many therapeutic options currently exist in alopecia areata, none of them are curative or preventive. Besides, none of them are approved by Food and Drug Administration (FDA). The disease unfortunately has an unpredictable course. The factors indicating a poor prognosis are the extent of hair loss at the presentation, long duration of the disease, and ophiasis pattern of hair loss. There are only a few randomized controlled studies conducted on recalcitrant AA. Recent research on immunology of hair follicle and recent developments in immunopathogenesis, together with the shared pathways of the disease with other autoimmune disorders, led investigators to focus on novel therapies that target specific immunological pathways. Herein, we will review shortly the current treatment options in recalcitrant alopecia areata based on recently published studies and then will focus on the recently developed broad-spectrum and targeted therapeutics.

Keywords: alopecia areata, refractory, treatment, new, biological treatment

1. Introduction

Alopecia areata (AA) is a common immune-mediated disorder [1]. It affects 0.1–0.2% of the general population and accounts for 0.7% to 3.8% of all patients attending to dermatology clinics [1, 2]. It affects both genders equally. Although onset may occur at any age, 60% of new cases had their first diagnosis before 20 years age [1, 2].

Despite its high prevalence, the exact cause and triggering factors of AA are still unknown [1–3]. It is considered to be a complex genetic, immune-mediated disease [1–5].
targets primarily hair follicles and characterized by dense peribulbar lymphocytic infiltrate [4, 6]. Hair follicle is a dynamic immune privileged “miniorgan” with unique immune and hormone microenvironments. This means that hair follicles are immune-protected sites with deficient major histocompatibility complex (MHC) expression [7, 8]. Evidence suggests that AA results from the loss of immune privilege with presentation of autoantigens, triggered by environmental factors in genetically susceptible individuals [1, 3, 7–9]. Many genes that are found to be associated with AA are also related to the immune system [3, 9]. Cytotoxic CD8+ NKG2D+ T cells are key players in the pathogenesis of AA that produce interferon-γ (IFN-γ) [5, 10]. Interleukin (IL)-2 and IL-15 are well known drivers of cytotoxic activity by IFN-γ-producing CD8+ T cells and natural killer (NK) cells [10]. Besides, recently published studies investigating the cytokine profile in lesional AA scalp indicates concurrent activation of Th1 and Th2 immune axes, as well as interleukin (IL)-23 and IL-32 cytokine pathways [11–13]. Also, in another recent study, it was supported that Th1-type cytokine profile is related to disease activity of AA, whereas Th2-type cytokines may be associated with the persistence of AA [14]. It is significant to understand both the pathomechanism of AA and responsible cytokines in order to develop new treatments for recalcitrant AA [3, 6, 7, 13].

In AA, most commonly affected area is the scalp [1, 2]. On scalp, it usually presents with well demarcated, one or more hairless patches with preserved follicular ostia and without erythema [1]. If 100% of the scalp hair is lost, it is named as alopecia totalis (AT). Any hair-bearing area such as beard, eyebrows, eyelashes, body, armpits, and pubic region may also be affected in AA, as well as the entire body, alopecia universalis (AU) [1, 2, 15]. Depending on the extent of involvement, AA can be associated with a dramatic reduction of quality of life [1, 2, 16, 17]. The association with other autoimmune diseases such as thyroid diseases, vitiligo, diabetes mellitus, pernicious anemia, rheumatoid arthritis may be seen with AA [2, 6, 17–19]. Atopy is twice as common in AA patients as it is in the general population [2, 16]. Other diseases and genetic disorders reported to be associated with AA include Down syndrome, Addison’s disease, autosomal recessive autoimmune polyglandular syndrome, psoriasis, lupus, ulcerative colitis, and multiple sclerosis. These less common disorders are more likely to be associated with AT and AU [2].

AA has an unpredictable outcome [1, 2, 16]. Up to 50% of patients with limited patchy AA will recover within 1 year even without treatment [16, 17]; while 7–10% of patients can eventually develop the severe chronic form of the condition, which is refractory to most of the treatments [20]. The factors indicating a poor prognosis are the extent of hair loss presentation (extensive AA/AT/AU), an ophiasis pattern of hair loss, onset in childhood, a long duration of hair loss, associated atopy or autoimmune disease [1, 16, 17, 19]. The chance of full recovery is less than 10% in AT/AU [2].

2. Treatment

2.1. Conventional therapies

For the disease of AA, there exists currently neither a universally proven therapy that induces and sustains remission, nor a cure [21]. Various treatments are available; however, only a few
randomized controlled studies in AA have been published [22]. Current treatment options include a variety of topical, intralesional, and systemic agents with the choice and recommendation based on the disease extent, duration of disease, associated disorders, and age of the patient [15, 23–25].

For recalcitrant AA, and particularly the AT and AU forms, finding appropriate therapeutics among currently available options is very challenging [13]. Current systemic treatment options mostly show limited efficacy and are often associated with major adverse effects in these cases [15, 24].

In this chapter, different treatment modalities in AA will be reviewed. As discussion of all the treatment modalities for AA is beyond the scope of this chapter, instead we rather focused our attention on current treatment regimens for recalcitrant and extensive AA, and on novel treatment modalities, which are still being under investigation.

2.1.1. Corticosteroids

2.1.1.1. Topical corticosteroids

Midpotent and potent topical corticosteroids (CSs) are usually used to treat AA, especially patchy type AA, but the evidence for their effectiveness is limited in recalcitrant AA [23–26]. CSs are thought to affect peribulbar lymphocytes and decrease inflammation around the bulb region, thereby allowing follicles to enter a normal hair cycle [25, 26].

2.1.1.2. Intralesional corticosteroids

For adult patients characterized with limited scalp involvement or in cases with involvement of eyebrows, intralesional corticosteroids (ILCSs) are considered as a first-line therapy [15, 21, 23]. Although, ILCSs have been used for about 50 years, no published randomized controlled trials have been found about this treatment in AA [22, 27].

2.1.1.3. Systemic corticosteroids

Systemic CSs are the most useful immunosuppressive therapy for patients with active AA [21, 23]. The suggested dosages for AA in adults are 1 mg/kg/day and 0.1–1 mg/kg/day for children. The dosages necessary to maintain hair regrowth in AA are daily between 30 mg and 150 mg [15]. However, there is little information available on the role of long-term use of systemic corticosteroids in chronic refractory AA [16, 24]. Combination with methotrexate (MTX) in the treatment of severe long-term AA might be more effective [28].

2.1.1.4. Systemic pulse corticosteroids

Systemic pulse corticosteroid therapy (PCT) is another choice in the treatment of recalcitrant and extensive AA [17, 23, 29]. The use of PCT was introduced to minimize the side effects associated with prolonged systemic corticosteroid therapy. However, placebo-controlled randomized studies with varying dosage schedules are required to standardize the treatment regimen, optimize the therapeutic efficacy, and evaluate the long-term outcomes [22, 24].
2.1.2. **Topical anthralin (dithranol)**

Although the mechanism of anthralin (dithranol) is unknown, the interaction of the drug with different cytokines such as IFNs, tumor necrosis factor (TNF), IL-1, and IL-10 points to a nonspecific immunomodulatory effect, which is responsible for regrowth [30]. There are a small number of uncontrolled case series [22, 30], in which, no randomized controlled study was found in recalcitrant AA.

2.1.3. **Topical immunotherapy (topical sensitizers)**

Topical immunotherapy (TI) with diphenylcyclopropenone (DPCP) or squaric acid dibutyl-ester (SADBE) is recommended as a first-line therapy in adult patients with AA having more than 50% scalp involvement [23, 30]. No randomized controlled trials have been found to evaluate the effectiveness of TI in recalcitrant AA [22, 31]. A review of all articles published on TI concluded that 50–60% of the patients experienced worthwhile regrowth, although the range of response was very broad (9–87%) [31–34].

2.1.4. **Topical minoxidil**

Minoxidil is a topical preparation, of which the mechanism of action is not fully understood. Vasodilatation, angiogenesis, enhanced cell proliferation at the base of the bulb and differentiation above the dermal papilla, and potassium channel opening have all been proposed [23]. It was confirmed that topical minoxidil may induce new hair growth in AA but less likely to do so in more severe and extensive diseases [23, 24, 35].

2.1.5. **Topical prostaglandin analogues**

Prostaglandin (PG) F2α and its analogues have been shown to have stimulatory effects on murine hair follicles and follicular melanocytes in both telogen and anagen phases and also on the stimulation of conversion from telogen to anagen phase [24]. Although reports about effective clinical response have been found [36], two randomized controlled studies demonstrated an efficacy of topical latanoprost in the AA [37–39].

2.1.6. **Topical bexarotene**

Bexarotene is a retinoid X receptor agonist that induces T-cell apoptosis and effects as an immunomodulator [23]. In a randomized half-head trial study including patients of recalcitrant AA treated with topical bexarotene, no difference was demonstrated between the two sides [40].

2.1.7. **Calcineurin inhibitors**

2.1.7.1. **Cyclosporine**

Cyclosporine (Cyc) is an immunosuppressive agent that inhibits helper T-cell activity and suppresses the IFN-γ production. The treatment with Cyc alone or in combination with systemic steroids demonstrated variable clinical results with a response rate between 25% and 88.4% [17, 41–43].
Despite these effective results, side effects of Cyc make this therapy not appropriate for the long-term use [21]. Neither pimecrolimus nor tacrolimus was shown to be effective in AA [44–46].

2.1.8. Methotrexate

Methotrexate (MTX) is an immunosuppressive agent and a folic acid antagonist, which exerts its effect by inhibiting DNA synthesis and has anti-inflammatory properties [23].

Although no randomized controlled study has been found, MTX and low doses of oral corticosteroids might be an effective treatment for resistant AA, which should be evaluated in larger series [28, 47, 48].

2.1.9. Azathioprine

Azathioprine (AZT) is a cytotoxic and immunosuppressive drug and has selective effects on T lymphocytes [17, 23]. An open-label uncontrolled study and a recently published prospective study suggested that AZT might be an alternative [49, 50].

2.1.10. Sulfasalazine

Sulfasalazine is an immunomodulatory and anti-inflammatory drug that inhibits the release of IL-2 and PGE2 and reduces the inflammatory cell chemotaxis and antibody production [51]. Several uncontrolled studies have interrogated the efficiency of the drug [51–53]. Although there are conflicting results and there is no randomized controlled study, sulfasalazine may be a hope for resistant and extensive cases. Additional larger studies should be conducted on this subject.

2.1.11. Simvastatin/ezetimibe

Statins are lipid-lowering drugs that also inhibit T-lymphocyte activation, downregulate expression of adhesion molecules, and have immunomodulatory effects [54]. Case series were reported demonstrating the efficiency of daily dosage of simvastatin 40 mg and ezetimibe 10 mg in AA [55–57]. Contrarily, Loi et al. reported a study of 20 patients (17 patients were evaluated) with recalcitrant AA, in which 14 of 17 were unresponsive [58]. All of these reports suggest that simvastatin/ezetimibe might be a promising agent in AA. Further randomized controlled studies are needed in recalcitrant AA.

2.1.12. Phototherapy

Having effects on Langerhans cells, cytokine profile, inducing apoptosis and promotion of immunosuppression make phototherapy a choice of treatment in AA [59]. There are several uncontrolled studies of psoralen plus ultraviolet A (PUVA) light with either oral or topical psoralens and either with local or whole body irradiation with response rates up to 60% in AA [60–62]. However, two retrospective reviews reported that PUVA is not an effective treatment method in AA [63, 64]. No randomized controlled trials for neither PUVA nor narrow band ultraviolet B (nbUVB) treatments have been found. A recent study suggested that the
combination therapy with topical Cyc and PUVA may be an additional choice for severe and recalcitrant AA [65]. Four patients were reported responding by both clinically and histopathologically to UVA1 therapy [66].

2.1.13. Laser therapy

Recently, there has been a great interest in the potential treating role of laser and light-based therapies in various disorders including AA [67–69]. A study which investigated the efficacy of pulsed diode laser (904 nm) in the treatment of resistant patchy AA reported a regrowth rate in 94% of the patients, while no response was shown in control patches [68].

The efficacy of excimer laser was investigated in various reports with a failure of regrowth [69–72].

2.1.14. Miscellaneous treatments

\textit{Inosiplex (Isoprinosine):} Inosiplex, an immunomodulator, was tried in a randomized controlled study with recalcitrant AA and significant regrowth was observed in the group treated with inosiplex [73].

\textit{Platelet-rich plasma (PRP):} There are reports showing the efficacy of PRP in extensive AA [74–76]. A case with ophiasis type AA was reported to be treated successfully with PRP [74]. A recently published randomized controlled study suggested that PRP might be a safe and effective treatment for AA [75].

2.2. Targeted therapies

In recent years, various biological agents that target pathogenesis have been introduced for the treatment of various diseases. Understanding the pathomechanism of AA has led investigators to do research about the efficacy of new biological treatments in AA. There are still multiple possible therapeutic targets being explored. After going through the above mentioned current treatments, the below section will focus on the recent broad-spectrum and targeted therapeutics, centering upon suggested AA immune pathways.

2.2.1. Tumor necrosis factor (TNF)-\(\alpha\) inhibitors

TNF-\(\alpha\) is a proinflammatory cytokine that mediates inflammation and has a role in cell proliferation and differentiation [77]. TNF-\(\alpha\) was shown to be elevated in the serum of patients with AA [78] and in lesional AA skin than nonlesional skin [12]. Although this evidence suggests that blocking TNF activity may improve AA, a clinical trial of 17 individuals was performed to investigate the effect of etanercept in AA. As a result of the study, it was found as ineffective [79]. Several reports have been published indicating the development of AA during a treatment of anti-TNF-\(\alpha\) for another disease [80–86]. Gorcey et al. reported a patient with AU, refractory to various treatment modalities, who was successfully treated with adalimumab, while being treated for the flare of atopic dermatitis [87].

Pharmacogenetics and the inherent physiologic levels of TNF may explain why TNF inhibitors cause AA in some individuals, while treating AA in others. These conclusions warrant further investigation on this subject.
2.2.2. **IL-23 pathway antagonism**

2.2.2.1. **Ustekinumab**

Ustekinumab is a human monoclonal IgG1 antibody that binds with the p40 subunit of IL-12 and IL-23 and inhibits their activity [88].

The Th17 immunologic pathway and associated cytokines including IL23 and IL17 are important in the pathophysiology of psoriasis, psoriatic arthritis, and other spondyloarthropathies [13, 89]. Many studies have demonstrated that IL-23 has an important role by driving the expansion and functional maintenance of Th17 development [90].

Suárez-Fariñas et al. performed a study on microarray and RT-PCR profile of 27 lesional and 17 nonlesional scalp samples from patients with AA and compared them with normal scalp samples (n=6). Genes associated with T-cell migration/activation were found to be significantly induced in lesional vs. nonlesional AA tissues. IL-12/23p40 showed the highest increase in mRNA expression of all measured inflammatory markers in lesional scalp of AA compared with normal scalp from healthy subjects [12]. As increased Th1 serum cytokine levels have been associated with extensive AA, IL-12 inhibitors (ustekinumab) would be expected to treat or at least to prevent hair loss [11, 91].

Guttman-Yassky et al. demonstrated hair regrowth in three extensive AA patients (one had AU) treated with 90 mg subcutaneously. At the 20th week, all patients exhibited varying degrees of hair regrowth. The patient with AU, with the highest baseline inflammation and lowest expression of hair keratins, exhibited the highest regrowth [92].

On the other hand, case reports of AA developing during treatment with ustekinumab for psoriasis have also been published [93–95].

Future clinical trials including larger samples are needed to clarify the clinical efficacy of ustekinumab in AA.

2.2.3. **Th17/IL-17 antagonism**

2.2.3.1. **Secukinumab**

Secukinumab is a recombinant, high-affinity, fully human IgG1κ monoclonal antibody that selectively inhibits IL-17A [12, 96, 97].

IL-17A is known to induce the expression of T-cell and dendritic cell chemokines, which lead to the migration of memory T cells and dendritic cells to the inflammation area [97].

Tanemura et al. found the infiltration of CD4(+)IL-17A(+) Th17 cells in the dermis, particularly around hair follicles, in all 4 cases in their study [98].

A recent study by Atwa et al. examined IL-17, IL-21, IL-22, IL-6, and TNF-α levels in the serum of patients with AA and studied their association with the clinical type and severity of AA. All of these cytokines were found to be significantly higher in the AA group than in the control group. Significant positive correlations between the serum IL-17 and disease severity, between the serum TNF-α and disease severity were detected. Also significant positive correlation between serum IL-22 and duration of AA was detected [99].
Lew et al. conducted a case-control association study of 238 AA patients, in which, IL17A and IL17RA (IL-17A receptor) gene polymorphisms were detected [100].

These studies support a possible role for an anti-IL-17 treatment in AA. Secukinumab is being tested in a double-blind, randomized, placebo-controlled clinical trial for AA (ClinicalTrials.gov NTC02599129).

2.2.4. Broad T-cell inhibition

2.2.4.1. Apremilast

Apremilast is an orally available molecule that inhibits phosphodiesterase 4 (PDE4) [13, 101]. It is approved in the treatment of psoriasis, psoriatic arthritis, and currently tested in trials for atopic dermatitis, and other inflammatory and dermatological conditions [102].

Inhibition of PDE4 leads to reduced production of proinflammatory mediators, such as TNF, IFN-γ, IL-12/23p40, IL-17A, and IL-22 [101, 102]. On the other hand, apremilast has been reported to increase the production of IL-6 and IL-10 [101–104]. This is of interest, since IL-10 is a cytokine with potent anti-inflammatory properties, while IL-6 is a cytokine with pro- and anti-inflammatory features [101]. Apremilast also exerts its effects by hydrolyzing cyclic adenosine monophosphate (cAMP) and thus affects various inflammatory mediators. PDE4 antagonism results in elevated intracellular cAMP [101–103].

In a study by Keren et al. PDE4 was found highly elevated in the lesions of AA in a mouse model of AA; apremilast was shown to be effective with almost complete preservation of hair follicles and resulted significant in reductions in inflammatory cytokines, such as PDEe, IFN-γ, and TNF-α [105]. Suárez-Fariñas et al. reported a highly increase of PDE4 in human AA lesions in their study [12]. In a further study by Guttman-Yassky et al., levels of PDE4 were found to decrease after treatment with IL-12/IL-23 antagonist [92].

Apremilast might be an appropriate therapeutic option for AA and is under being investigation as a clinical trial (ClinicalTrials.com NCT02684123).

2.2.4.2. Janus kinase inhibitors

Janus kinase (JAK) inhibitors are potent antiinflammatory and antiproliferative agents [13, 106]. Tofacitinib is a pan-JAK inhibitor that is approved by the FDA for the treatment of rheumatoid arthritis and ruxolitinib is a JAK1/2 inhibitor that is approved for the treatment of polycythemia vera and myelofibrosis [107].

JAK family of protein-tyrosine kinases is made of four members: JAK1, JAK2, JAK3 and TYR2 (Tyrosine kinase2). The JAK/STAT pathway transduces extracellular signals from a variety of cytokines, growth factors and hormones to the nucleus and is responsible for the expression of thousands of protein-encoding genes [107, 108]. Targeting JAK1 or JAK2 was thought to be helpful for interfering with the signaling pathways implicated in the generation of pathogenic Th1 and Th17 cells in autoimmunity [106].

The possibility of reversal of AA by JAK inhibitors was successfully shown in murine model by blocking IFN-γ and interleukin-2 (IL-2) or IL-15 receptor β and by reducing the
accumulation of CD8 + T cells [10, 109, 110]. Both JAK1 and JAK2 (ruxolitinib, baricitinib) and JAK3 (tofacitinib) inhibitors have been reported to effectively treat AA in various case reports [109–112].

Craiglow and King reported a patient with psoriasis who also had long standing AU. After 8 months of treatment with tofacitinib, the patient had full regrowth of hair on scalp along with significant regrowth on eyelashes, eyebrows and other body sides [111].

Jabbari et al. studied the effect of tofacitinib by clinically and by the changes in expression of AA-associated genes in skin as well as circulating CXCL10 levels with result of significant hair growth along with change in skin and biochemical markers [109].

Gupta et al. reported two cases of recalcitrant AU treated with tofacitinib. Both cases showed full regrowth of hair on the body at the end of 8 months of treatment [112].

A case with AU treated with tofacitinib with a transient efficacy has also been reported [113].

Today, there are ongoing clinical trials for tofacitinib (ClinicalTrials.gov NCT02312882, NCT02197455, NCT02299297 and NCT02812342), ruxolitinib (NCT01950780), and baricitinib in the treatment of AA and in various inflammatory diseases, which will make us understand the exact effect of these treatments [13].

Topical JAK inhibitors have also been shown as effective in AD, psoriasis, dry eye disease and in allergic contact dermatitis model [114–117]. Topical JAK inhibitors may offer a good treatment option for especially for limited AA [13].

JAK inhibitors may replace some immunosuppressive treatments. Further clinical trials are warranted to clarify the exact effects of JAK inhibitors in AA.

2.2.4.3. Abatacept

Abatacept is a fusion protein of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) with a portion of IgG1 (CTLA-4Ig) that selectively modulates T-cell co-stimulation. It binds to CD80/CD86 receptors on antigen-presenting cells and by this way blocks the interaction of CD80/86 with CD28 which is found on T-cells and inhibits full T-cell activation [118, 119]. In vitro, abatacept decreases T-cell proliferation, the production of inflammatory cytokines such as IFN-γ, TNF-α and IL-2 and B-cell immunological response [118]. Also, it was found to increase Treg cells, which was linked to downregulation of activation-associated marker molecules [120]. Abatacept is currently being used in rheumatoid arthritis with FDA approval [13]. Since T-cell activation is crucial in the development of AA [9], there is a potential chance for abatacept in the treatment of AA. There is an ongoing study for abatacept (ClinicalTrials.gov NCT02018042).

2.2.5. IL-2 modulation as a modifier of regulatory function

2.2.5.1. Aldesleukin

Aldesleukin is a recombinant interleukin-2 (IL-2) molecule and a biological response modifier having various immunomodulatory properties [121]. Aldesleukin is currently approved only for treatment of renal cell carcinoma and metastatic melanoma and is usually used in high
doses in these indications [122, 123]. It can be applied via intravenous or subcutaneous administration. In high intravenous bolus regimen, it has been reported to be highly toxic [121]. IL-2 is a key cytokine for T regulatory (reg) cell differentiation, homeostasis and functions [124]. In AA, an imbalance in the immune state of patients has been detected with altered T-helper cell and Treg cell functions [125, 126]. A study by Shin et al. revealed impaired function of CD4 T reg cells [127]. A study by Castela et al. evaluated the efficacy of low dose recombinant IL-2 treatment on five AA patients. Four of five patients had partial regrowth and the improvement continued up to 6 months after drug cessation. Pre and posttreatment biopsies were taken to compare the level of T reg cells and an increase was detected in posttreatment group [128]. Aldesleukin is now being under investigation and clinical studies with larger samples are needed to assess the exact efficacy of the drug (ClinicalTrials.gov NCT01840046).

2.2.6. Th2 pathway inhibition

2.2.6.1. Dupilumab

Dupilumab is a fully human monoclonal antibody directed against the α subunit of IL-4 receptor. It blocks the signaling of IL-4 and IL-13, both of which are the key cytokines in Th2-mediated pathways [13, 129]. The efficacy of dupilumab has been studied in atopic dermatitis (AD) and asthma with a rapid, significant clinical improvement [129–133]. Also, decreasing in the levels of serum and skin Th2 markers and Th17/IL-23 associated markers have been demonstrated [129].

Several studies support a shared genetic background between AA and AD, besides both diseases were shown to have upregulation of Th2 component and an IL-23 [12, 134, 135]. The history of atopy and autoimmune disease was also found to be associated with an increased risk of AA [2, 16, 136].

Suarez-Farinas et al. reported a study of 22 patients who also had AD. They sought a detailed molecular profile of the lesional and nonlesional AA transcriptomes with AA. A significant upregulation of Th2 cytokine IL-13 was found similar to AD lesions. A possible pathogenic role of Th2 axis in patients with AA was supported as a result of this study [12].

Fuentes-Duculan et al. studied pre- and posttreatment lesional biopsies of 6 patients with patchy AA and performed immunohistochemistry and gene expression analysis. They found a significant expression of inflammatory markers of IL-2, IL-15, Th1 and Th2 (IL-13, CCL17 and CCL18), IL-12/IL-23p40 before treatment. After treatment with intralesional corticosteroid injection, a significant downregulation was observed in IL-12/IL-23p40, CCL18 [11].

Sharing possible common pathways both in AA and AD make dupilumab also worth triable in AA.

2.2.6.2. Tralokinumab

Tralokinumab is an IgG4 humanized monoclonal antibody that targets neutralising IL-13 [13, 137]. IL-13 is a Th2 cell cytokine and has an important role in atopy [137]. Tralokinumab is under investigation for asthma and AD (ClinicalTrials.gov NC). As mentioned above,
Suárez-Fariñas et al. found the highest levels of IL-13 and IL23p40 mRNA expressions in lesional vs. nonlesional AA and in lesional AA vs. healthy subjects [12]. Tembhre et al. found significant high levels of IL-13 and IL-17A which suggested altered Th cell function [125].

These findings support a possible role of tralokinumab in AA which is now being under investigation (ClinicalTrials.gov NCT02684097).

3. Conclusions

Currently, many therapies are available and the treatment depends on many factors, such as the severity, extent, duration of the disease, and age of the patient.

Although many treatments are shown to be effective in extensive recalcitrant AA, the most important problems of the present studies include the limited number of randomized controlled studies, lack of evaluating the long-term efficacy and follow-up, small number of participants, and significant disease heterogeneity in patient selection.

Better understandings of the immunopathological mechanisms responsible in AA have led the clinical researches to develop better therapeutic options for AA. However, future larger studies are needed to clarify the immunological pathways responsible in AA, which will lead to further therapeutic developments.

Author details

Arzu Kılıç

*Address all correspondence to: kilicarzu@gmail.com

Department of Dermatology, Balikesir University School of Medicine, Cagis Yerleskesi, Balikesir, Turkey

References

[1] Perera E, Yip L, Sinclair R. Alopecia areata. Curr Probl Dermatol. 2015; 47: 67–75. DOI: 10.1159/000369406

[2] Alkhalifah A, Alsantali A, Wang E, McElwee KJ, Shapiro J. Alopecia areata update. Part I. Clinical picture, histopathology, and pathogenesis. J Am Acad Dermatol. 2010; 62: 177–88. DOI: 10.1016/j.jaad.2009.10.032

[3] Biran R, Zlotogorski A, Ramot Y. The genetics of alopecia areata: new approaches, new findings, new treatments. J Dermatol Sci. 2015; 78: 11–20. DOI: 10.1016/j.jdermsci.2015.01.004
McElwee KJ, Tobin DJ, Bystryn JC, King LE Jr, Sundberg JP. Alopecia areata: an autoimmune disease? Exp Dermatol. 1999; 8:371–9.

McElwee KJ, Gilhar A, Tobin DJ, Ramot Y, Sundberg JP, Nakamura M, Bertolini M, Inui S, Tokura Y, King LE Jr, Duque-Estrada B, Tosti A, Keren A, Itami S, Shoenfeld Y, Zlotogorski A, Paus R. What causes alopecia areata? Exp Dermatol. 2013; 22: 609–26.

Hordinsky MK. Overview of alopecia areata. Invest Dermatol Symp Proc. 2013; 16: S13-5. DOI: 10.1038/jidsymp.2013.4

Ito T. Recent advances in the pathogenesis of autoimmune hair loss disease alopecia areata. Clin Dev Immunol. 2013; 2013: 348546.

Ito T. Hair follicle is a target of stress hormone and autoimmune reactions. J Dermatol Sci. 2010; 60: 67–73. DOI: 10.1016/j.jdermsci.2010.09.006

Gilhar A, Kalish RS. Alopecia areata: a tissue specific autoimmune disease of the hair follicle. Autoimmun Rev. 2006; 5: 64-9. DOI: 10.1016/j.autrev.2005.07.001

Xing L, Dai Z, Jabbari A, Cerise JE, Higgins CA, Gong W, de Jong A, Harel S, De Stefano GM, Rothman L, Singh P, Petukhova L, Mackay-Wiggan J, Christiano AM, Clynes R. Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition. Nat Med. 2014; 20: 1043–9. DOI: 10.1038/nm.3645

Fuentes-Duculan J, Gulati N, Bonifacio KM, Kunjravia N, Zheng X, Suárez-Fariñaz M, Shemer A, Guttman-Yassky E, Krueger JG. Biomarkers of alopecia areata disease activity and response to corticosteroid treatment. Exp Dermatol. 2016; 25: 282–6.

Suárez-Fariñaz M, Ungar B, Noda S, Shroff A, Mansouri Y, Fuentes-Duculan J, Czernik A, Zheng X, Estrada YD, Xu H, Peng X, Shemer A, Krueger JG, Lebwohl MG, Guttman-Yassky E. Alopecia areata profiling shows TH1, TH2, and IL-23 cytokine activation without parallel TH17/TH22 skewing. J Allergy Clin Immunol. 2015; 136:1277–87. DOI: 10.1016/j.jaci.2015.06.032

Renert-Yuval Y, Guttman-Yassky E. A novel therapeutic paradigm for patients with extensive alopecia areata. Expert Opin Biol Ther. 2016; 16: 1005–14. DOI: 10.1080/14712598.2016.1188076

Zhang X, Zhao Y, Ye Y, Li S, Qi S, Yang Y, Cao H, Yang J, Zhang X. Lesional infiltration of mast cells, Langerhans cells, T cells and local cytokine profiles in alopecia areata. Arch Dermatol Res. 2015; 307: 319-31. DOI: 10.1007/s00403-015-1539-1

Wasserman D, Guzman-Sanchez DA, Scott K, McMichael A. Alopecia areata. Int J Dermatol. 2007; 46: 121-31. DOI: 10.1111/j.1365-4632.2007.03193.x

Finner AM. Alopecia areata: clinical presentation, diagnosis, and unusual cases. Dermatol Ther. 2011; 24: 348-54. DOI: 10.1111/j.1529-8019.2011.01413.x
[17] Alkhalifah A. Alopecia areata update. Dermatol Clin. 2013; 31: 93–108. DOI: 10.1016/j.det.2012.08.010

[18] Goh C, Finkel M, Christos PJ, Sinha AA. Profile of 513 patients with alopecia areata: associations of disease subtypes with atopy, autoimmune disease and positive family history. J Eur Acad Dermatol Venereol. 2006; 20: 1055–60. DOI: 10.1111/j.1468-3083.2006.01676.x

[19] Tosti A, Bellavista S, Iorizzo M. Alopecia areata: a long term follow-up study of 191 patients. J Am Acad Dermatol. 2006; 55: 438–41. DOI: 10.1016/j.jaad.2006.05.008

[20] Madani S, Shapiro J. Alopecia areata update. J Am Acad Dermatol. 2000; 42: 549–66

[21] Shapiro J. Current treatment of alopecia areata. J Invest Dermatol Symp Proc. 2013; 16: S42-4. DOI: 10.1038/jidsymp.2013.14

[22] Delamere FM, Sladden MM, Dobbins HM, Leonardi-Bee J. Interventions for alopecia areata. Cochrane Database Syst Rev. 2008; 2: CD004413. DOI: 10.1002/14651858.CD004413.pub2

[23] Alkhalifah A, Alsantali A, Wang E, McElwee KJ, Shapiro J. Alopecia areata update: part II. Treatment. J Am Acad Dermatol. 2010; 62: 191-202. DOI: 10.1016/j.jaad.2009.10.031

[24] Messenger AG, McKillop J, Farrant P, McDonagh AJ, Sladden M. British association of dermatologists’ guidelines for the management of alopecia areata 2012. Br J Dermatol. 2012; 166: 916–26. DOI: 10.1111/j.1365-2133.2012.10955.x

[25] Hordinsky M, Donati A. Alopecia areata: an evidence-based treatment update. Am J Clin Dermatol. 2014; 15: 231–46. DOI: 10.1007/s40257-014-0086-4

[26] Inui S, Itami S. Contact immunotherapy-resistant alopecia areata totalis/universalis reactive to topical corticosteroid. J Dermatol. 2015; 42: 937–9. DOI: 10.1111/1346-8138.12938

[27] Kassim JM, Shipman AR, Szczecinska W, Siah TW, Lam M, Chalmers J, Macbeth AE. How effective is intralesional injection of triamcinolone acetonide compared with topical treatments in inducing and maintaining hair growth in patients with alopecia areata? A Critically Appraised Topic. Br J Dermatol. 2014; 170: 766–71. DOI: 10.1111/bjd.12863

[28] Joly P. The use of methotrexate alone or in combination with low doses of oral corticosteroids in the treatment of alopecia totalis or universalis. J Am Acad Dermatol. 2006;55 :632-6.

[29] Seo J, Lee YI, Hwang S, Zheng Z, Kim DY. Intramuscular triamcinolone acetonide: an undervalued option for refractory alopecia areata. J Dermatol. 2016 Jul 23. DOI: 10.1111/1346–8138.13533
[30] Fiedler-Weiss VC, Buys CM. Evaluation of anthralin in the treatment of alopecia areata. Arch Dermatol. 1987; 123: 1491–3.

[31] Hill ND, Bunata K, Hebert AA. Treatment of alopecia areata with squaric acid dibutyl-ester. Clin Dermatol. 2015; 33: 300–4. DOI: 10.1016/j.clindermatol.2014.12.001

[32] Wiseman MC, Shapiro J, MacDonald N, Lui H. Predictive model for immunotherapy of alopecia areata with diphencyprone. Arch Dermatol. 2001; 137: 1063–8.

[33] Avgerinou G, Gregoriou S, Rigopoulos D, Stratigos A, Kalogeromitros D, Katsambas A. Alopecia areata: topical immunotherapy treatment with diphencyprone. J Eur Acad Dermatol Venereol. 2008; 22: 320–3. DOI: 10.1111/j.1468-3083.2007.02411.x

[34] Durdu M, Özcan D, Baba M, Seçkin D. Efficacy and safety of diphenylcyclopropenone alone or in combination with anthralin in the treatment of chronic extensive alopecia areata: a retrospective case series. J Am Acad Dermatol. 2015; 72: 640–50. DOI:10.1016/j.jaad.2015.01.008

[35] Fransway AF, Muller SA. 3 percent topical minoxidil compared with placebo for the treatment of chronic extensive alopecia areata. Cutis. 1988; 41: 431–5.

[36] Coronel-Pérez IM, Rodríguez-Rey EM, Camacho-Martínez FM. Latanoprost in the treatment of eyelash alopecia in alopecia areata universalis. J Eur Acad Dermatol Venereol. 2010; 24: 481–5. DOI: 10.1111/j.1468-3083.2009.03543.x

[37] Ross EK, Bolduc C, Lui H, Shapiro J. Lack of efficacy of topical latanoprost in the treatment of eyebrow alopecia areata. J Am Acad Dermatol. 2005; 53: 1095–6. DOI: 10.1016/j.jaad.2005.06.031

[38] Roseborough I, Lee H, Chwalek J, Stamper RL, Price VH. Lack of efficacy of topical latanoprost and bimatoprost ophthalmic solutions in promoting eyelash growth in patients with alopecia areata. J Am Acad Dermatol. 2009; 60: 705–6. DOI: 10.1016/j.jaad.2008.08.029

[39] Ahsan MK, Urano Y, Kato S, Oura H, Arase S. Immunohistochemical localization of thyroid hormone nuclear receptors in human hair follicles and in vitro effect of L-triiodothyronine on cultured cells of hair follicles and skin. J Med Invest. 1998; 44: 179–84.

[40] Talpur R, Vu J, Bassett R, Stevens V, Duvic M. Phase I/II randomized bilateral half-head comparison of topical bexarotene 1% gel for alopecia areata. J Am Acad Dermatol. 2009; 61: 592.e1-9. DOI: 10.1016/j.jaad.2009.02.037

[41] Gupta AK, Ellis CN, Cooper KD, Nickoloff BJ, Ho VC, Chan LS, Hamilton TA, Tellner DC, Griffiths CE, Voorhees JJ. Oral cyclosporine for the treatment of alopecia areata. A clinical and immunohistochemical analysis. J Am Acad Dermatol. 1990; 22: 242–50.

[42] Kim BJ, Min SU, Park KY, Choi JW, Park SW, Youn SW, Park KC, Huh CH. Combination therapy of cyclosporine and methylprednisolone on severe alopecia areata. J Dermatolog Treat. 2008; 19: 216–20. DOI: 10.1080/09546630701846095
[43] Açıkgöz G, Çalışkan E, Tunca M, Yeniay Y, Akar A. The effect of oral cyclosporine in the treatment of severe alopecia areata. Cutan Ocul Toxicol. 2014; 33: 247-52. DOI: 10.3109/15569527.2013.839997

[44] Ucak H, Kandi B, Cicek D, Halisdemir N, Dertlioglu SB. The comparison of treatment with clobetasol propionate 0.05% and topical pimecrolimus 1% treatment in the treatment of alopecia areata. J Dermatolog Treat. 2012; 23: 410–20. DOI: 10.3109/09546634.2011.590788

[45] Rigopoulos D, Gregoriou S, Korfitis C, Gintzou C, Vergou T, Katrinaki A, Kalogeromitros D. Lack of response of alopecia areata to pimecrolimus cream. Clin Exp Dermatol. 2007; 32: 456–7. DOI: 10.1111/j.1365-2230.2007.02367.x

[46] Hunter N, Shaker O, Marei N. Diphencyprone and topical tacrolimus as two topical immunotherapeutic modalities. Are they effective in the treatment of alopecia areata among Egyptian patients? A study using CD4, CD8 and MHC II as markers. J Dermatolog Treat. 2011; 22: 2–10. DOI: 10.3109/09546630903410182

[47] Anuset D, Perceau G, Bernard P, Reguiai Z. Efficacy and safety of methotrexate combined with low- to moderate-dose corticosteroids for severe alopecia areata. Dermatology. 2016; 232: 242–8. DOI: 10.1159/000359205

[48] Droitcourt C, Milpied B, Ezzedine K, Hubiche T, Belin E, Akpadjan F, Taieb A, Seneschal J. Interest of high-dose pulse corticosteroid therapy combined with methotrexate for severe alopecia areata: a retrospective case series. Dermatology. 2012; 224: 369–73. DOI: 10.1159/000339341

[49] Farshi S, Mansouri P, Safar F, Khiabanloo SR. Could azathioprine be considered as a therapeutic alternative in the treatment of alopecia areata? A pilot study. Int J Dermatol. 2010; 49: 1188–93. DOI: 10.1111/j.1365-4632.2010.04576.x

[50] Vañó-Galván S, Hermosa-Gelbard Á, Sánchez-Neila N, Miguel-Gómez L, Saceda-Corrado D, Rodrigues-Barata R, Jaén P. Treatment of recalcitrant adult alopecia areata universalis with oral azathioprine. J Am Acad Dermatol. 2016; 74: 1007–8. DOI: 10.1016/j.jaad.2015.12.055

[51] Rashidi T, Mahd AA. Treatment of persistent alopecia areata with sulphasalazine. Int J Dermatol. 2008; 47: 850–2. DOI: 10.1111/j.1365-4632.2008.03700.x

[52] Rashid S, Ahsan U, Saeed W. Efficacy and safety of sulphasalazine in treatment of alopecia areata. J Pakistan Assoc Dermatol. 2015; 25: 298–302.

[53] Bakar O, Gurbuz O. Is there a role for sulphasalazine in the treatment of alopecia areata? J Am Acad Dermatol. 2007; 57: 703–6.

[54] Namazi MR. Statins: novel additions to the dermatologic arsenal? Exp Dermatol. 2004; 13: 337–9.

[55] Robins DN. Case reports: alopecia universalis: hair growth following initiation of simvastatin and ezetimibe therapy. J Drugs Dermatol. 2007; 6: 946–7.
[56] Ali A, Martin JM 4th. Hair growth in patients alopecia areata totalis after treatment with simvastatin and ezetimibe. J Drugs Dermatol. 2010; 9: 62–4.

[57] Lattouf C, Jimenez JJ, Tosti A, Miteva M, Wikramanayake TC, Kittles C, Herskovitz I, Handler MZ, Fabbrocini G, Schachner LA. Treatment of alopecia areata with simvastatin/ezetimibe. J Am Acad Dermatol. 2015; 72: 359–61. DOI: 10.1016/j.jaad.2014.11.006

[58] Loi C, Starace M, Piraccini BM. Alopecia areata (AA) and treatment with simvastatin/ezetimibe: experience of 20 patients. J Am Acad Dermatol. 2016; 74: e99-e100. DOI: 10.1016/j.jaad.2015.09.071

[59] Walker D, Jacobe H. Phototherapy in the age of biologics. Semin Cutan Med Surg. 2011; 30: 190–8. DOI: 10.1016/j.sder.2011.08.004

[60] Taylor CR, Hawk JL. PUVA treatment of alopecia areata partialis, totalis and universalis: audit of 10 years’ experience at St John’s Institute of Dermatology. Br J Dermatol. 1995; 133: 914–8.

[61] Claudy AL, Gagnaire D. PUVA treatment of alopecia areata. Arch Dermatol. 1983; 119: 975–8.

[62] Healy E, Rogers S. PUVA treatment for alopecia areata—does it work? A retrospective review of 102 cases. Br J Dermatol. 1993; 129: 42–4.

[63] Park KY, Jang WS, Son IP, Choi SY, Lee MY, Kim BJ, Kim MN, Ro BI. Combination therapy with cyclosporine and psoralen plus ultraviolet a in the patients with severe alopecia areata: a retrospective study with a self-controlled design. Ann Dermatol. 2013; 25: 12–6. DOI: 10.5021/ad.2013.25.1.12

[64] Herz-Ruelas ME, Welsh O, Gomez-Flores M, Welsh E, Miranda-Maldonado I, Ocampo-Candiani J. Ultraviolet A-1 phototherapy as an alternative for resistant alopecia areata. Int J Dermatol. 2015; 54: e445-7. DOI: 10.1111/ijd.13054

[65] Tzung TY, Chen CY, Tzung TY, Kao FJ, Chen WC. Infrared irradiation as an adjuvant therapy in recalcitrant alopecia areata. Dermatol Surg. 2009; 35: 721–3. DOI: 10.1111/j.1524-4725.2009.01120.x

[66] Waiz M, Saleh AZ, Hayani R, Jubory SO. Use of the pulsed infrared diode laser (904 nm) in the treatment of alopecia areata. J Cosmet Laser Ther. 2006; 8: 27–30. DOI: 10.1080/14764170600607368

[67] Zakaria W, Passeron T, Ostovari N, Lacour JP, Ortonne JP. 308-nm excimer laser therapy in alopecia areata. J Am Acad Dermatol. 2004; 51: 837–8. DOI: 10.1016/j.jaad.2004.05.026
[70] Gundogan C, Greve B, Raulin C. Treatment of alopecia areata with the 308-nm xenon chloride excimer laser: case report of two successful treatments with the excimer laser. Lasers Surg Med. 2004; 34: 86–90. DOI: 10.1002/lsm.20002

[71] Al-Mutairi N. 308-nm excimer laser for the treatment of alopecia areata. Dermatol Surg. 2007; 33: 1483–7. DOI: 10.1111/j.1524-4725.2007.33320.x

[72] Al-Mutairi N. 308-nm excimer laser for the treatment of alopecia areata in children. Pediatr Dermatol. 2009; 26: 547–50. DOI: 10.1111/j.1525-1470.2009.00980.x

[73] Georgala S, Katoulis AC, Befon A, Georgala K, Stavropoulos PG. Inosiplex for treatment of alopecia areata: a randomized placebo-controlled study. Acta Derm Venereol. 2006; 86: 422–4. DOI: 10.2340/00015555-0138

[74] Donovan J. Successful treatment of corticosteroid-resistant ophiasis-type alopecia areata (AA) with platelet-rich plasma (PRP). JAAD Case Rep. 2015; 1: 305–7. DOI: 10.1016/j.jdcr.2015.07.004

[75] Trink A, Sorbellini E, Bezzola P, Rodella L, Rezzani R, Ramot Y, Rinaldi F. A randomized, double-blind, placebo- and active-controlled, half-head study to evaluate the effects of platelet-rich plasma on alopecia areata. Br J Dermatol. 2013; 169: 690–4. DOI: 10.1111/bjd.12397

[76] Singh S. Role of platelet-rich plasma in chronic alopecia areata: our centre experience. Indian J Plast Surg. 2015; 48: 57–9. DOI: 10.4103/0970-0358.155271

[77] Zaba LC, Suarez-Farinaz M, Fuentes-Duculan J, Nograles KE, Guttman-Yassky E, Cardinale I, Lowes MA, Krueger JG. Effective treatment of psoriasis with etanercept is linked to suppression of IL-17 signaling, not immediate response TNF genes. J Allergy Clin Immunol. 2009; 124: 1022–10. DOI: 10.1016/j.jaci.2009.08.046

[78] Kasumagic-Halilovic E, Prohic A, Cavaljuga S. Tumor necrosis factor-alpha in patients with alopecia areata. Indian J Dermatol. 2011; 56: 494–6. DOI: 10.4103/0019-5154.87124

[79] Strober BE, Siu K, Alexis AF, Kim G, Washenik K, Sinha A, Shupack JL. Etanercept does not effectively treat moderate to severe alopecia areata: an open-label study. J Am Acad Dermatol. 2005; 52: 1082–4. DOI: 10.1016/j.jaad.2005.03.039

[80] Garcia Bartels N, Lee HH, Worm M, Burmester GR, Sterry W, Blume-Peytavi U. Development of alopecia areata universalis in a patient receiving adalimumab. Arch Dermatol. 2006; 142: 1654–5. DOI: 10.1001/archderm.142.12.1654

[81] Chaves Y, Duarte G, Ben-Said B, Tebib J, Berard F, Nicolas JF. Alopecia areata universalis during treatment of rheumatoid arthritis with anti-TNF-alpha antibody (adalimumab). Dermatology. 2008; 217: 380. DOI: 10.1159/000162180

[82] Le Bidre, Chaby G, Martin L, Perrussel M, Sassoulas B, Sigal ML, Kaass C, Lespessailles E, Nseir A, Estève E. Alopecia areata during anti-TNF alpha therapy: nine cases. Ann Dermatol Venereol. 2011; 138: 285–93. DOI: 10.1016/j.annder.2011.01.047

[83] Pan Y, Rao NA. Alopecia areata during etanercept therapy. Ocul Immunol Inflamm. 2009; 17: 127–9. DOI: 10.1080/09273940802596559
[84] Pelivani N, Hassan AS, Braathen LR, Hunger RE. Alopecia areata universalis elicited during treatment with adalimumab. Dermatology. 2008; 216: 320–3. DOI: 10.1159/000113945

[85] Tauber M, Buche S, Reygagne P, Berthelot JM, Aubin F, Ghislain PD, Cohen JD, Coquerelle P, Goujon E, Jullien D, Brixi H, Jeudy G, Guennoc X, Martin A, Brénaut E, Hoppé E, Bertolotti A, Bardin T, Delaporte E, Allez M, Bachelez H, Seneschal J, Viguier M, Groupe de Recherche sur Psoriasis de Société Française de, Dermatologie, Club Rhumatismes et Inflammation (CRI), Groupe d'études thérapeutiques des affections inflammatoires du tube digestif (GETAID). Alopecia areata occurring during anti-TNF therapy: a national multicenter prospective study. J Am Acad Dermatol. 2014; 70: 1146–9. DOI: 10.1016/j.jaad.2014.03.005

[86] Ferran M, Calvet J, Almirall M, Pujol RM, Maymó J. Alopecia areata as another immune-mediated disease developed in patients treated with tumour necrosis factor-α blocker agents: report of five cases and review of the literature. J Eur Acad Dermatol Venereol. 2011; 25: 479–84. DOI: 10.1111/j.1468-3083.2010.03770.x

[87] Gorcey L, Gordon Spratt EA, Leger MC. Alopecia universalis successfully treated with adalimumab. JAMA Dermatol. 2014; 150: 1341–4. DOI: 10.1001/jamadermatol.2014.1544

[88] Meng Y, Dongmei L, Yanbin P, Jinju F, Meile T, Binzhu L, Xiao H, Ping T, Jianmin L. Systematic review and meta-analysis of ustekinumab for moderate to severe psoriasis. Clin Exp Dermatol. 2014; 39: 696–707. DOI: 10.1111/ced.12390

[89] Mease PJ. Inhibition of interleukin-17, interleukin-23 and the TH17 cell pathway in the treatment of psoriatic arthritis and psoriasis. Curr Opin Rheumatol. 2015; 27: 127–33. DOI: 10.1097/BOR.0000000000000147

[90] Johnsson HJ, McInnes IB. Interleukin-12 and interleukin-23 inhibition in psoriatic arthritis. Clin Exp Rheumatol. 2015; 33: S115-8.

[91] Barahmani N, Lopez A, Babu D, Hernandez M, Donley SE, Duvic M. Serum T helper 1 cytokine levels are greater in patients with alopecia areata regardless of severity or atopy. Clin Exp Dermatol. 2010; 35: 409–16. DOI: 10.1111/j.1365-2230.2009.03523.x

[92] Guttmann-Yassky E, Ungar B, Noda S, Suprun M, Shooff A, Dutt R, Khattri S, Min M, Mansouri Y, Zheng X, Estrada YD, Singer GK, Suarez-Farinas M, Krueger JG, Lebwohl MG. Extensive alopecia areata is reversed by IL-12/IL-23p40 cytokine antagonism. J Allergy Clin Immunol. 2016; 137: 301–4. DOI: 10.1016/j.jaci.2015.11.001

[93] Verros C, Rallis E, Crowe M. Letter: alopecia areata during ustekinumab administration: co-existence or an adverse reaction?. Dermatol Online J. 2012; 18: 14.

[94] Słowińska M, Kardynal A, Warszawik O, Czuwara J, Rudnicka L. Alopecia areata developing parallel to improvement of psoriasis during ustekinumab therapy. J Dermatol Case Rep. 2010; 4: 15–7. DOI: 10.3315/jdcr.2010.1041
[95] Tauber M, Beneton N, Reygagne P, Bachelez H, Viguier M. Alopecia areata developing during ustekinumab therapy: report of two cases. Eur J Dermatol. 2013; 23: 912–3. DOI: 10.1684/ejd.2013.2221

[96] Garnock-Jones KP. Secukinumab: a review in moderate to severe plaque psoriasis. Am J Clin Dermatol. 2015; 16: 323–30. DOI: 10.1007/s40257-015-0143-7

[97] Gaspari AA, Tyring S. New and emerging biologic therapies for moderate-to-severe plaque psoriasis: mechanistic rationales and recent clinical data for IL-17 and IL-23 inhibitors. Dermatol Ther. 2015; 28: 179–93. DOI: 10.1111/dth.12251

[98] Tanemura A, Oiso N, Nakano M, Itoi S, Kawada A, Katayama I. Alopecia areata: infiltration of Th17 cells in the dermis, particularly around hair follicles. Dermatology. 2013; 226: 333–6. DOI: 10.1159/000350933

[99] Atwa MA, Youssef N, Bayoumy NM. T-helper 17 cytokines (interleukins 17, 21, 22, and 6, and tumor necrosis factor-α) in patients with alopecia areata: association with clinical type and severity. Int J Dermatol. 2016; 55: 666–72. DOI: 10.1111/ijd.12808

[100] Lew BL, Cho HR, Haw S, Kim HJ, Chung JH, Sim WY. Association between IL17A/IL17RA gene polymorphisms and susceptibility to alopecia areata in the Korean population. Ann Dermatol. 2012; 24: 61–5. DOI: 10.5021/ad.2012.24.1.61

[101] Forchhammer S, Ghoreschi K. Update on the treatment of psoriasis and psoriatic arthritis-role of apremilast. Psoriasis: Targets and Therapy. 2015; 15: 125–8.

[102] Poole RM, Ballantyne AD. Apremilast: first global approval. Drugs. 2014; 74: 825–37. DOI: 10.1007/s40265-014-0218-4

[103] Schafer PH, Day RM. Novel systemic drugs for psoriasis: mechanism of action for apremilast, a specific inhibitor of PDE4. J Am Acad Dermatol. 2013; 68: 1041–2. DOI: 10.1016/j.jaad.2012.10.064

[104] Schafer PH, Parton A, Gandhi AK, Capone L, Adams M, Wu L, Bartlett JB, Loveland MA, Gilhar A, Cheung YF, Baillie GS, Houslay MD, Man HW, Muller GW, Stirling DI. Apremilast, a cAMP phosphodiesterase-4 inhibitor, demonstrates anti-inflammatory activity in vitro and in a model of psoriasis. Br J Pharmacol. 2010; 159: 842–55. DOI: 10.1111/j.1476-5381.2009.00559.x

[105] Keren A, Shemer A, Ullmann Y, Paus R, Gilhar A. The PDE4 inhibitor, apremilast, suppresses experimentally induced alopecia areata in human skin in vivo. J Dermatol Sci. 2015; 77: 74–6. DOI: 10.1016/j.jdermsci.2014.11.009

[106] Ghoreschi K, Gadina M. Jakpot! New small molecules in autoimmune and inflammatory diseases. Exp Dermatol. 2014; 23: 7–11. DOI: 10.1111/exd.12265

[107] Seavey MM, Dobrzanski P. The many faces of Janus kinase. Biochem Pharmacol. 2012; 83: 1136–45. DOI: 10.1016/j.bcp.2011.12.024
[108] Roskoski R Jr. Janus kinase (JAK) inhibitors in the treatment of inflammatory and neoplastic diseases. Pharmacol Res. 2016; **111**: 784–803. DOI: 10.1016/j.phrs.2016.07.038

[109] Jabbari A, Nguyen N, Cerise JE, et al. Treatment of an alopecia areata patient with tofacitinib results in regrowth of hair and changes in serum and skin biomarkers. Exp Dermatol. 2016; **25**: 642–3. DOI: 10.1111/exd.13060

[110] Jabbari A, Dai Z, Xing L, et al. Reversal of alopecia areata following treatment with the JAK1/2 inhibitor baricitinib. EBioMedicine. 2015; **2**: 351–5. DOI: 10.1016/j.ebiom.2015.02.015

[111] Craiglow BG, King BA. Killing two birds with one stone: oral tofacitinib reverses alopecia universalis in a patient with plaque psoriasis. J Invest Dermatol. 2014; **134**: 2988–9. DOI: 10.1038/jid.2014.260

[112] Gupta AK, Carviel JL, Abramovits W. Efficacy of tofacitinib in treatment of alopecia universalis in two patients. J Eur Acad Dermatol Venereol. 2016; **30**: 1373–8. DOI:10.1111/jdv.13598

[113] Anzengruber F, Maul JT, Kamarachev J, et al. Transient efficacy of tofacitinib in alopecia areata universalis. Case Rep Dermatol. 2016; **8**: 102–6. DOI: 10.1159/000445182

[114] Bissonnette R, Papp KA, Poulin Y, Gooderham M, Raman M, Mallbris L, Wang C, Purohit V, Mamolo C, Papacharalambous J, Ports WC. Topical tofacitinib for atopic dermatitis: a phase 2a randomised trial. Br J Dermatol. 2016. Doi: 10.1111/bjd.14871. [Epub ahead of print]

[115] Ports WC, Khan S, Lan S, Lamba M, Bolduc C, Bissonnette R, Papp K. A randomized phase 2a efficacy and safety trial of the topical Janus kinase inhibitor tofacitinib in the treatment of chronic plaque psoriasis. Br J Dermatol. 2013; **169**: 137–45. DOI: 10.1111/bjd.12266

[116] Liew SH, Nichols KK, Klamerus KJ, Li JZ, Zhang M, Foulks GN. Tofacitinib (CP-690,550), a Janus kinase inhibitor for dry eye disease: results from a phase 1/2 trial. Ophthalmology. 2012; **119**: 1328–35. DOI: 10.1016/j.ophtha.2012.01.028

[117] Fukuyama T, Ehling S, Cook E, Bäumer W. Topically administered Janus-Kinase inhibitors tofacitinib and oclacitinib display impressive antipruritic and anti-inflammatory responses in a model of allergic dermatitis. J Pharmacol Exp Ther. 2015; **354**: 394–405. DOI: 10.1124/jpet.115.223784

[118] Herrero-Beaumont G, Martínez Calatrava MJ, Castañeda S. Abatacept mechanism of action: concordance with its clinical profile. Reumatol Clin. 2012; **8**: 78–83. DOI: 10.1016/j.reuma.2011.08.002

[119] Furst DE, Breedveld FC, Kalden JR, Smolen JS, Burmester GR, Emery P, Keystone EC, Schiff MH, van Riel PL, Weinblatt ME, Weisman MH. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2006. Ann Rheum Dis. 2006;**65**:iii2-15. DOI: 10.1136/ard.2006.061937
[120] Bonelli M, Göschl L, Blüml S, Karonitsch T, Hirahara K, Ferner E, Steiner CW, Steiner G, Smolen JS, Scheinecker C. Abatacept (CTLA-4Ig) treatment reduces T cell apoptosis and regulatory T cell suppression in patients with rheumatoid arthritis. Rheumatology (Oxford). 2016; 55: 710–20. DOI: 10.1093/rheumatology/kev403

[121] Noble S, Goa KL. Aldesleukin (recombinant interleukin-2). BioDrugs. 1997; 7: 394–422.

[122] Schmidinger M, Hejma M, Zielinski CC. Aldesleukin in advanced renal cell carcinoma. Expert Rev Anticancer Ther. 2004; 4: 957–80. DOI: 10.1586/14737140.4.6.957

[123] Atkins MB, Lotze MT, Dutcher JP, Fisher RI, Weiss G, Margolin K, Abrams J, Sznol M, Parkinson D, Hawkins M, Paradise C, Kunkel L, Rosenberg SA. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. J Clin Oncol. 1999; 17: 2105–6.

[124] Klatzmann D, Abbas AK. The promise of low-dose interleukin-2 therapy for autoimmune and inflammatory diseases. Nat Rev Immunol. 2015; 15: 283–94. DOI: 10.1038/nri3823

[125] Tembhre MK, Sharma VK. T-helper and regulatory T-cell cytokines in the peripheral blood of patients with active alopecia areata. Br J Dermatol. 2013; 169: 543–8. DOI: 10.1111/bjd.12396

[126] Han YM, Sheng YY, Xu F, Qi SS, Liu XJ, Hu RM, Miao Y, Huang GQ, Yang QP. Imbalance of T-helper 17 and regulatory T cells in patients with alopecia areata. J Dermatol. 2015; 42: 981–8. DOI: 10.1111/1346-8138.12978

[127] Shin BS, Furuhashi T, Nakamura M, Torii K, Morita A. Impaired inhibitory function of circulating CD4+CD25+ regulatory T cells in alopecia areata. J Dermatol Sci. 2013; 70: 141–3. DOI: 10.1016/j.jdermsci.2013.01.006

[128] Castela E, Le Duff F, Butori C, Ticchioni M, Hofman P, Bahadoran P, Lacour JP, Passeron T. Effects of low-dose recombinant interleukin 2 to promote T-regulatory cells in alopecia areata. JAMA Dermatol. 2014; 150: 748–51. DOI: 10.1001/jamadermatol.2014.504

[129] Beck LA, Thaçi D, Hamilton JD, Graham NM, Bieber T, Rocklin R, Ming JE, Ren H, Kao R, Simpson E, Ardeleanu M, Weinstein SP, Pirozzi G, Guttmann-Yassky E, Suárez-Fariñas M, Hager MD, Stahl N, Yancopoulos GD, Radin AR. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med. 2014; 371: 130–9. DOI: 10.1056/NEJMo31314768

[130] Simpson EL, Bieber T, Eckert L, Wu R, Ardeleanu M, Graham NM, Pirozzi GM, Mastey V. Patient burden of moderate to severe atopic dermatitis (AD): insights from a phase 2b clinical trial of dupilumab in adults. J Am Acad Dermatol. 2016; 74: 491–8. DOI: 10.1016/j.jaad.2015.10.043

[131] Thaçi D, Simpson EL, Beck LA, Bieber T, Blauvelt A, Papp K, Soong W, Worm M, Szepietowski JC, Sofen H, Kawashima M, Wu R, Weinstein SP, Graham NM, Pirozzi G, Teper A, Sutherland ER, Mastey V, Stahl N, Yancopoulos GD, Ardeleanu M. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inade-
quately controlled by topical treatments: a randomised, placebo-controlled, dose-rang-
ing phase 2b trial. Lancet. 2016; 387: 40–52. DOI: 10.1016/S0140-6736(15)00388-8

[132] Chung KF. Dupilumab: a potential new treatment for severe asthma. Lancet. 2016; 388: 3–4. DOI: 10.1016/S0140-6736(16)30311-7

[133] Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B, Pirozzi G,Sutherland ER, Evans RR, Joish VN, Eckert L, Graham NM, Stahl N, Yancopoulos GD, Louis-Tisserand M, Teper A. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-rang-
ing trial. Lancet. 2016; 388: 31–44. DOI: 10.1016/S0140-6736(16)30307-5

[134] Chu SY, Chen YJ, Tseng WC, Lin MW, Chen TJ, Hwang CY, Chen CC, Lee DD, Chang YT, Wang WJ, Liu HN. Comorbidity profiles among patients with alopecia areata: the importance of onset age, a nationwide population-based study. J Am Acad Dermatol. 2011; 65: 949–56. DOI: 10.1016/j.jaad.2010.08.032

[135] Gilhar A, Etzioni A, Paus R. Alopecia areata. N Engl J Med. 2012; 366:1515–25. DOI: 10.1056/NEJMra1103442

[136] Barahmani N, Schabath MB, Duvic M, National Alopecia Areata Registry. History of atopy or autoimmunity increases risk of alopecia areata. J Am Acad Dermatol. 2009; 61: 581–91. DOI: 10.1016/j.jaad.2009.04.031

[137] Hussein YM, Ahmad AS, Ibrahim MM, Elsherbeny HM, Shalaby SM, El-Shal AS, Sabbah NA. Interleukin 13 receptors as biochemical markers in atopic patients. J Investig Allergol Clin Immunol. 2011; 21: 101–7.