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New Modalities in the Treatment of Refractory Alopecia Areata

Arzu Kılıç

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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]. It

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 histocompability 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+ Tcells 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

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].

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)-α inhibitors

TNF-α is a proinflammatory cytokine that mediates inflammation and has a role in cell proliferation and differentiation [77]. TNF-α 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-α 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 usteukinumab 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 furher 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 therapeutical 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 sof 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 approvement [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 (ClinicalTrais.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.

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