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Dupilumab and Alopecia Areata: A Possible Combined or Disturbance Therapy? A Review of The Literature

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ABSTRACT

Introduction: Dupilumab, a monoclonal antibody targeting IL-4 receptor subunit alpha, treats atopic dermatitis (AD) and may impact alopecia areata (AA). AA involves Th1-driven immune activity, and recent studies suggest a role for Th2 pathways. Dupilumab's effects on AA are mixed, with reports of both improvement and worsening.

Objectives: This study aims to review the effects of dupilumab on AA in patients with AD, analyzing literature to understand cases of improvement or worsening and identifying contributing factors.

Methods: A literature review was conducted using articles in platforms such as PubMed, Scopus, and Web of Science written up to April 2024, focusing on studies involving AA, AD, and dupilumab. Articles were analyzed for patient demographics, disease characteristics, and responses to treatment.

Results: Out of 35 articles reviewed, 13 AA cases worsened after dupilumab (mean age 32.8; mostly males with patchy alopecia), and 38 cases showed improvement (mean age 27.6; majority females, varying AA types). Full hair regrowth occurred in 11 improved cases, while 9 had partial regrowth.

Conclusions: Dupilumab shows dual effects on AA, influenced by Th1/Th2 immune profiles. Worsening was more common in males with Th1-driven AA, while females with Th2-skewed AA saw improvement. Factors like age, disease severity, and IgE levels may affect outcomes, suggesting a need for personalized treatment approaches for AA patients with AD.

Introduction

Dupilumab is a monoclonal antibody that targets IL-4 receptor subunit alpha (IL-4R-alpha), a shared component of IL-4 and IL-13 receptors; these cytokines have a pivotal role in Th2-driven inflammation. Dupilumab has been approved for the treatment of moderate-to-severe atopic dermatitis (AD) however, recently, it has shown efficacy in other conditions, such as alopecia areata (AA) [1]. AA is an autoimmune non-scarring alopecia that can affect any hair-bearing area. The (IFN)γ/Th1 pathway and the Janus kinase (JAK) signaling pathway are the main protagonists of hair follicle immune aggression in AA, although recent studies have shown a co-participation of Th2-axis cytokines [2].

The possible association between AD and AA has already been published, and for this reason, many cases have been described about the use of dupilumab in patients with both dermatological diseases [3]. The literature shows that dupilumab may have a double effect on patients affected by AA and AD: it has been reported that it may promote AA development as well as hair re-growth, something that could be related to a specific pattern of cytokines associated with AA inflammatory background [4,5].

Objectives

We conducted a literature review to define the different effects of dupilumab in patients with AA. More specifically, we wanted to review the current literature on the topic so as to understand any proven relationship between dupilumab administration and improvement/worsening of AA in patients with AD.

Furthermore, to the best of our knowledge, we wanted to report all the similar cases that could strengthen such duality in dupilumab use.

Lastly, we wanted to analyze the data found and draw conclusions on the topic, based on the existing evidence, as previously stated.

Methods

We performed a literature review using the medical databases PubMed, Scopus, and Web of Science. We included keywords "dupilumab", "alopecia areata", and "atopic dermatitis". We included articles written up to April 2024. Selected articles were based on relevance, focusing on case reports, reviews, and original articles. Articles that did not provide relevant information or were not written in English were excluded. Subsequently, we collected all data on patients demographic characteristics, disease profile, and personal response to dupilumab. Finally, we divided our findings into two different categories based on how dupilumab affected AA patients (Tables 1 and 2).

Results

Our review of the literature yielded important findings regarding the dual efficacy of dupilumab in patients affected with AA and AD. We found and analyzed a total of 35 relevant articles (Tables 1 and 2). Among these, 13 cases of AA worsened after dupilumab (M = 8; F = 5; Mean Age = 32.8), whilst 38 cases of AA improved after dupilumab (M = 18; F = 20; mean age = 27.6).

The clinical characteristics of AA in patients who worsened after starting dupilumab were mostly of a patchy alopecias (n = 9), with three diffuse forms and one case of AA in androgenetic alopecia pattern. Six patients had complete regrowth after discontinuation of dupilumab, whilst three patients had only partial regrowth. Two patients were still under treatment at the moment of the publication of the studies, and two patients had no information about AA evolution after the modification of dupilumab therapy (Table 1).

Regarding the cohort of patients that experienced hair regrowth after starting dupilumab, eleven patients had alopecia areata universalis (AAU), nine patients had alopecia areata totalis (AAT), three patients had alopecia areata subtotalis (AA with a SALT score greater than 80% and less than 100%), and 15 patients had a patchy alopecia. Eleven patients were associated with full regrowth, whereas nine patients reported partial regrowth (one of them had a worsening of AA partial regrowth after dupilumab suspension) (Table 2).

Discussion

The results of our literature review provide interesting insights into the dual impact of dupilumab on patients affected by AA and AD. We reviewed 35 relevant articles exploring the relationship between these conditions and the role of dupilumab (Tables 1 and 2). Our analysis revealed that 13 cases of AA worsened after starting dupilumab, whereas 38 cases of AA showed improvement (Tables 1 and 2). This showcases how the efficacy of dupilumab in AA can be variable, likely due to individual factors. Patients who experienced a worsening of their condition were predominantly male, with patchy alopecia. The worsening typically began around 17 weeks after starting the drug; however, some of these patients experienced hair regrowth after discontinuing dupilumab (Table 1). On the other hand, patients who showed improvement in AA after starting dupilumab were mostly female, with a broader range of severity (from patchy alopecia to AAU). A significant number of these patients experienced full hair regrowth, suggesting that dupilumab could help promote hair regrowth in specific AA cases (Table 2) [6-36].

Dupilumab provides a distinct perspective on the interplay between AA and AD. The literature suggests that this

Table 1. Cases of AA Worsening after Dupilumab.

No of patients	Sex (M/F)	Age	Clinical characteristics of AA/onset after dupilumab	Clinical course after steroid treatment/CyA/dupilumab discontinuation	Reference
1	M	29	AA in patches – 5 weeks	Partial regrowth (undergoing treatment at the moment of the publication of the article)	Mitchell K et al. (2018)
1	M	31	AA in patches on the anterior scalp – 6 weeks	Undergoing treatment at the moment of the publication of the article	Barroso-Garcia et al. (2018)
1	M	33	Diffuse AA in the frontal and occipital region + beard – 7 weeks	Complete hair regrowth after 3 months	Salguero-Fernandez et al. (2018)
1	M	24	AA in patches – 1 week	Partial regrowth after 3 weeks (ketoconazole 3% shampoo was used)	Yazdanyar S et al. (2019)
1	F	23	AA in patches in the frontal, vertex and occipital areas – 48 hours	Complete regrowth after 6 months (dupilumab was discontinued)	Barbarin C et al. (2019)
1	M	27	AA in the vertex and temporal areas – 18 weeks	Complete regrowth after 2 months (dupilumab was discontinued)	Flanagan K et al. (2019)
1	M	35	AA in patches, mostly in the parietal, occipital and frontal regions – 6 weeks	Partial regrowth (78%) after 4 months	Kanda N et al. (2019)
1	M	53	AA in patches – 1 year	Complete regrowth after 4 months (dupilumab was discontinued, and Cya was started)	Stander S et al. (2020)
1	F	42	AA in androgenetic alopecia pattern – 4 months	Complete regrowth after 2 months	Carnicle J et al (2021)
1	F	45	AA in oval patches in the occipital region + two small patches in the temporal region – 1 year	Complete hair regrowth after 2 months	Beaziz J et al. (2021)
2	F = 2	16.5 (mean age)	Mean SALT = 91.5	1 patient reached SALT 100 (starting from SALT98 after 5 months of therapy); the other patient reached SALT98 (starting from SALT85 after 2 months of therapy).	McKenzie et al. (2021)
1	M	36	AA of the beard – 25 weeks	Information not available in the article	Chromy D et al. (2023)

drug can have a dual effect on these conditions, possibly due to its suppression of Th2-axis inflammation [6-36]. On this matter, recent research indicates that AA may be linked to two distinct pathogenetic pathways: a Th1-skewed and a Th2-skewed mechanism [3]. The existence of two different pathways may explain the opposing responses to dupilumab observed in AA patients. In individuals with Th2-skewed AA, inhibiting Th2 inflammation with dupilumab can lead to hair regrowth. However, for patients with Th1-skewed AA, dupilumab-induced suppression of Th2 may exacerbate Th1-driven inflammation, resulting in hair loss [37-39]. Additionally, Marks et al. observed that female patients are more likely to have a Th2-skewed condition, while males are more often associated with a Th1-skewed condition. This is also demonstrated by our data, as the cohort of patients who improved were predominantly female (Th2-skewed), and those who worsened were mostly male (Th1-skewed) [37]. Future research could focus on better identifying the underlying pathogenic mechanism in AA patients, leading to patient-tailored treatment.

Dupilumab has shown efficacy in treating AA in children (< 18 years old); indeed, as displayed in our dataset, 16 children experienced hair regrowth after taking dupilumab, while only McKenzie et al. reported two patients with worsening

Table 2. Cases of AA Improved after Dupilumab.

No of patients	Sex (M/F)	Age (years)	Baseline clinical characteristics	Clinical Course after Dupilumab onset	Reference
1	F	13	AAT	Regrowth on 60% of scalp	Penzi LR et al. (2018)
1	F	49	AAU	Full regrowth after 8 months	Alniemi DT et al. (2018)
1	M	28	AA subtotalis (SALT score 87,4) in an AD patient (EASI score: 14.9 - IgE = 11.987 IU/mL)	Full regrowth at month 6 and AD scores were significantly reduced (EASI score: 6.5)	Darrigade A-S et al. (2018)
1	F	35	AAU	Full regrowth after 12 months	Smogorzewski J et al. (2019)
1	F	25	AAT	Almost full regrowth after 11 months	Aszodi N et al. (2019)
2	M - M	38 - 32	AAU – AA with ophiasis pattern	Full regrowth – full regrowth	Ludriksone L et al. (2019)
1	M	44	AA in focal patches (SALT 61.6) in an atopic dermatitis patient (EASI score: 46.7 - IgE = 44300 IU/mL)	Almost full regrowth and improvement of the skin manifestations (in 3 months EASI score: 25)	Uchida H et al. (2019)
1	M	49	AA in focal patches	Full regrowth after 3 months	Magdaleno-Tapial J et al. (2019)
1	F	33	AA in patches complicated with trichotillomania in an atopic dermatitis patient (EASI score: 46)	Almost complete regrowth after 19 weeks. The patient's skin condition had also improved (EASI score: 9.6).	Ushida M et al. (2020)
7	F = 2; M = 5	40 (mean age)	Mean SALT = 79.2 (Mean EASI = 39.93; Mean IgE = 10794.7 UI/mL)	Mean SALT of 28.5 after treatment - median duration of 24 weeks)	Harada K et al. (2020)
1	F	13	AAT	Full regrowth after 4 months (minimal eyelash and eyebrow regrowth)	Gruenstein D et al. (2020)
1	F	34	AAU	Complete regrowth of course terminal hair on the scalp, face, forearms, pubic area, and legs after 10 months	Call JE et al. (2020)
1	F	30	AAT in an atopic dermatitis patient (EASI score: 36)	Complete regrowth after 3 months and an improvement in AD (EASI score: 9.6)	Szekely S et al. (2020)
1	F	21	AAU	Partial regrowth with a single patch left after 4 months	Alotaibi et al. (2021)

5	M = 3; F = 2	12.8 (mean age)	57 (mean SALT)	1 patient went from SALT25 to SALT0 after 12 months of therapy; 1 patient went from SALT35 to SALT8 after 7 months of therapy; 1 patient went from SALT100 to SALT98 after 12 months of therapy; 1 patient went from SALT100 to SALT50 after 11 months of therapy; 1 patient went from SALT25 to SALT0 after 12 months of therapy.	McKenzie et al. (2021)
1	F	46	AAU	Partial regrowth of the face, scalp, and lower legs	Reinhold L et al. (2022)
1	M	16	AAT	Complete regrowth after 3 years	Kulkarni M et al. (2022)
5	M = 2; F = 3	4.6 (mean age)	Mean SALT = 60.8	4 patients reached SALT 0, and 1 patient reached SALT20. (No time-of-treatment is given for the 5 patients). Three out of 6 were simultaneously treated with oral minoxidil + topical tofacitinib, topical minoxidil + topical tofacitinib and pulsed prednisone + oral minoxidil, respectively.	Cho et al. (2023)
1	F	9	AA subtotalis - SALT score 98 (IgE = 999.6 IU/mL)	Hair regrowth, together with repigmentation of regrown white terminal hair de novo without disturbing the anagen phase of hair follicles.	Yan X et al. (2023)
1	F	4	AAU	Partial regrowth of the hair; eyebrows and eyelashes fully restored	Cai L et al. (2023)
1	F	45	AAU	Regrowth after 6 months (it is not specified in the article if partial or complete response)	McFeely O. (2023)
1	M	1	AAU	Partial regrowth	Tancredi V et al. (2024)
1	M	12	AA with ophiasis pattern	Complete regrowth after 2 months	Gualdi G et al. (2024)

conditions [38]. This is consistent with prior reports that link such variability to severe and/or long-standing AA [37]; indeed, these variants seem to be related to a higher chance of improvement after dupilumab administration. Additionally, it seems that dupilumab is associated with a slow onset of action in children and works better when combined with other therapies such as oral minoxidil [38,39].

Lastly, another factor that may be linked to the varying response to dupilumab in AA patients could be IgE levels. Indeed, Guttman-Yassky et al. conducted a Phase 2a clinical trial and noted that progress rates were higher in patients with baseline IgE levels of 200 IU/ml or more, demonstrating how a Th2-directed therapy could be beneficial for specific AA patients [1]. Although not many articles in our review reported IgE levels, all patients with high IgE levels improved significantly, which aligns with the literature [1].

We identified two potential limitations of this study that we would like to state. The first is represented by a possible selection bias due to a greater propensity to publish positive results of dupilumab on alopecia areata. The second is the absence of an indication for dupilumab for alopecia areata, making its use more difficult in patients affected solely by alopecia areata.

Conclusion

In conclusion, our research highlights once more the important yet intricate relationship linking AA, AD, and dupilumab. While the pathogenesis of AA is still debated, our findings underscore the existence of Th1-skewed and Th2-skewed AA subtypes. Additionally, we identified how different factors, such as sex, age, severity, and disease duration, might affect the response of AA patients to dupilumab. This is of paramount importance as it underscores the need to consider comorbidities in AA patients, especially those dealing with both AA and AD. Future studies are necessary to determine how different cytokine pathways underlying AA can influence dupilumab's effect, with the ultimate goal of creating more personalized and effective treatment protocols.

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