



Long-Term Effectiveness and Discontinuation Rates of Dupilumab in Atopic Dermatitis: A Comprehensive Literature Review

Hala Abdelaziz Fathallah Abdelkarem Mohamed^{a++*}

^a Medcare Women and Children Hospital, United Arab Emirates.

Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Background: Dupilumab, an IL-4 and IL-13 antagonist, has demonstrated efficacy in treating moderate-to-severe atopic dermatitis (AD). While short-term benefits are well-documented, long-term effectiveness and safety data are crucial for evaluating sustained treatment strategies.

Literature Review: A comprehensive review was conducted of studies evaluating dupilumab's impact on patient-reported outcomes and clinical measures over various periods. Key outcomes included the Eczema Area and Severity Index (EASI), Numerical Rating Scale (NRS) for pruritus, Dermatology Life Quality Index (DLQI), and treatment satisfaction. Long-term studies indicated that dupilumab remains effective and well-tolerated over extended periods. Significant improvements in EASI scores, pruritus, and quality of life were maintained or enhanced over 36 months. Patient satisfaction remained high, with a majority reporting substantial improvement in itch (75.3%) and

⁺⁺ Specialist Dermatology;

*Corresponding author: E-mail: halaabdelazizfathallah@gmail.com;

satisfactory disease control (80.7%). Discontinuation rates varied, with 23.8% of patients stopping treatment, primarily due to adverse events or perceived ineffectiveness. The most common adverse event was conjunctivitis. Real-world data also showed a high persistence rate, with improved compliance noted when patients administered their injections at home. Additionally, combined topical and systemic treatments were suggested as a beneficial approach for sustained management.

Conclusion: Dupilumab offers sustained benefits for managing moderate-to-severe atopic dermatitis, with ongoing improvements in disease control and quality of life. Despite some discontinuations related to adverse effects and inefficacy, the overall safety profile remains favorable.

Keywords: Dupilumab; atopic dermatitis; effectiveness.

1. INTRODUCTION

AD is a prevalent inflammatory skin condition that many individuals experience [1]. This condition is described as having a long-lasting and recurring nature, with episodes of itchy eczematous lesions appearing on dry skin [2]. The occurrence of AD has been on the rise in various parts of the world and has now stabilized in North America and Europe [3]. In children, the prevalence has reached 15-20%, while in adults it stands at 1-3% [3]. One of the main symptoms of AD is itching, which can greatly impact a person's quality of life [4, 5].

The pathophysiology of atopic dermatitis is a complex and multifactorial process [6]. It involves changes in the immune response, defects in the skin's protective barrier, genetic disorders, changes in the immune response, and environmental factors that disrupt the balance of microbes on the skin [7]. These factors contribute to abnormalities in the immune dysfunction and skin barrier, which are believed to play a crucial role in the development of atopic dermatitis [7].

Dupilumab, a fully human monoclonal antibody, has been approved in the US to treat symptoms of moderate-to-severe AD in both adults and pediatric patients aged 6 months and older [8]. It is specifically indicated for cases where topical prescription therapies are not effectively controlling the disease or are not recommended [8]. Given that AD is a chronic condition, it is crucial to assess the long-term effects of treatment and whether it provides sustained benefits, particularly from the patient's point of view [9]. Although a clinical trial's open-label extension demonstrated that dupilumab remained effective and safe for up to 4 years, there have been limited real-world studies that thoroughly assess the long-term patient experience with dupilumab [10]. These studies

either had a small sample size or followed patients for only 1 to 2 years. The long-term effectiveness of dupilumab and the implications of discontinuation are critical areas of interest for both clinicians and patients. While initial studies and clinical trials have demonstrated significant improvements in disease severity and quality of life, understanding the sustained efficacy of the medication and the consequences of stopping treatment are essential for optimizing patient outcomes [11-15].

This literature review aims to explore the long-term effectiveness of dupilumab in managing atopic dermatitis, drawing on data from clinical trials and real-world studies. Additionally, it will examine the factors influencing the discontinuation of dupilumab.

2. LITERATURE REVIEW

2.1 Long-Term Effectiveness of Dupilumab in Patients with Atopic Dermatitis

2.1.1 Patient reported outcomes

A study assessed patient-reported outcomes during long-term dupilumab treatment and evaluated data [8]. There were significant reductions from baseline in the use of concomitant AD therapy ($P < 0.05$). Between 30-36 months, the results for various factors such as sleep symptoms, flares, non-itch skin symptoms, health-related quality of life work/activity impairment, treatment satisfaction, and disease control were either similar to or even better than the results at the 12-month mark. These improvements were significant compared to the initial baseline measurements ($P < 0.001$). A majority of respondents, 75.3%, reported a significant improvement in itch due to global change. The majority of respondents, about

80.7%, reported satisfactory disease control (score of 7 on ADCT). Additionally, a high percentage of 86.8% expressed their satisfaction with the treatment.

Overall, the survey results showed that patients experienced ongoing benefits from long-term treatment with dupilumab, even up to 36 months. However, the use of additional therapies for atopic dermatitis (AD) did have a reducing effect.

A RELIEVE-AD was a study conducted to assess the effectiveness of dupilumab in adults with moderate-to-severe atopic dermatitis in real-world clinical practice settings [10]. The study used patient-reported outcomes to evaluate the impact of dupilumab over a period of one year. Patients in RELIEVE-AD experienced significant and long-lasting improvements in disease control, quality of life, and daily activities (including work productivity) throughout the course of one year of treatment. They also reported reductions in flares, itch, non-itch skin symptoms, and sleep problems. Additionally, the use of other therapies for AD decreased while patient satisfaction with treatment increased.

There is limited long-term data on the safety and long-term effectiveness of Dupilumab in treating atopic dermatitis. A study assessed the effectiveness and safety of dupilumab over a period of three years following the start of treatment [15]. The clinic and patient-reported outcomes were assessed over a period of three years, with evaluations conducted every four months. The study included a cohort of 418 patients. There was a noticeable decrease in the mean EASI over time, starting at 23.64 at baseline and reaching 2.31 at T9. There were similar trends in the reported outcomes of patients. At T1 (4 months), 75.58% of patients achieved EASI75 and 53.49% achieved EASI90. By T9, these numbers increased to 92.55% and 80.85% respectively. Additionally, 61.7% of patients achieved a DLQI score of 0/1 at T9. At T9, a majority of the patients (86 out of 94) achieved a mean NRSpp ≤ 4 , which is quite impressive. Conjunctivitis was the most frequently reported adverse event, affecting approximately 13% of patients at each timepoint analyzed. In clinical practice, Dupilumab has been shown to be both effective and safe for the treatment of AD for up to 3 years.

Silverberg et al. [16] and Dal Bello et al. [17] found that Dupilumab had a high persistence rate in real-world settings, suggesting that patients

were satisfied with its treatment schedule, tolerability, and effectiveness [16, 17]. In certain countries, there are still numerous patients who undergo Dupilumab injections at a clinic or hospital. In a recent study by Ito et al. [18], they found that the compliance rate significantly improved when patients were taught to administer their own injections of dupilumab at home [18].

2.1.2 Real world data on long term effectiveness

In a recent study by Halling et al. [19], they conducted a thorough analysis and review of real-world data to evaluate the safety and effectiveness of dupilumab in individuals with AD [19]. In real-world data, it has been shown that dupilumab is a well-tolerated therapy and highly effective for AD, similar to what was observed in clinical trials. However, some reports suggest that dupilumab may be slightly less effective in real-world settings compared to clinical trials. In routine clinical practice, the long-term effectiveness of therapy is closely tied to how committed patients are to staying on their prescribed treatment. Persistence in therapy refers to the duration of time from when treatment begins to when it is stopped.

2.2 Discontinuation of Dupilumab in Patients with Atopic Dermatitis

There is a lack of extensive data regarding the safety and long-term effectiveness of Dupilumab for atopic dermatitis in real-world scenarios. An investigation assessed the clinical effectiveness and factors leading to the discontinuation of Dupilumab treatment in individuals of different age groups who have AD. The study examined up to 5 years of treatment in real-world scenarios. A total of 1286 patients diagnosed with AD received treatment with Dupilumab. The majority of patients were able to keep their AD under control, with EASI scores of 7 or lower and NRS scores for pruritus of 4 or lower. These results were consistent over a period of up to 5 years of treatment, with percentages ranging from 78.6% to 92.3% for EASI scores and 72.2% to 88.2% for NRS scores. Additionally, a significant portion of patients (up to 70.5%) were able to extend the time between doses, typically to 300 mg every 3 or 4 weeks. There were some noticeable differences between age groups in terms of IGA and EASI over time, but these differences were relatively small. There were no significant differences in the reported levels of

itching between different age groups. The levels of median thymus- and activation-related chemokine showed a significant decrease from 1751 pg/mL to 390 after 6 months of treatment and continued to remain low. There was a temporary increase in median eosinophil levels up to week 16, followed by a significant decrease over time. A total of 306 patients, accounting for 23.8% of the study population, stopped taking Dupilumab. This occurred after a median duration of 54.0 weeks, with a range of 29.0 to 110.0 weeks. The most commonly cited reasons for discontinuation were adverse events, reported by 98 patients (7.6%), and ineffectiveness, reported by 85 patients (6.6%). A total of forty-one patients (3.2%) resumed treatment with Dupilumab, and the majority of these patients experienced a positive response once again. During this cohort study, the clinical effectiveness of Dupilumab remained consistent over a period of up to 5 years. Additionally, a significant number of patients were able to reduce their dosing interval to every 3 or 4 weeks. A significant number of patients had to stop their treatment, primarily because of adverse events and/or lack of effectiveness.

A study explored patient characteristics, effectiveness, safety, and treatment aspects of Dupilumab treatment for a duration of up to 84 weeks [20]. At 84 weeks, we observed a decrease of -15.2 (SE, 1.7) for the Eczema Area and Severity Index, -16.9 (SE, 1.4) for the Patient-Oriented Eczema Measure, and -17.2 (SE, 1.6) for the Dermatology Life Quality Index. We observed a positive trend in the improvement of the Investigator Global Assessment and Numerical Rating Scale for pruritus over time. A total of 79 severe adverse events were reported, with 11 of them being classified as serious. These events were observed in 69 patients. A total of 46 eye complaints were reported. A total of twenty-one patients made changes to their regular dosing schedule, while fourteen patients decided to stop treatment, primarily because it was not effective (n = 7).

Regularly practicing Dupilumab treatment for up to 84 weeks is generally well-tolerated, with the exception of some reported eye complaints. You may find that combining topical and initial concomitant systemic treatment can be a beneficial long-term solution for atopic dermatitis. This approach has been shown to provide sustained improvement in signs, symptoms, and overall quality of life.

3. CONCLUSION

The extensive data reviewed on the long-term effectiveness and discontinuation of dupilumab in patients with atopic dermatitis highlights its sustained efficacy and safety in real-world settings. Dupilumab consistently demonstrates significant improvements in patient-reported outcomes, such as reductions in Eczema Area and Severity Index (EASI) scores, pruritus, and overall quality of life, even up to 36 months and beyond. The ability of patients to extend dosing intervals further underscores the treatment's long-term effectiveness. However, the data also reveals important insights into the challenges associated with dupilumab therapy. While the majority of patients experienced continued benefits, a notable proportion discontinued treatment primarily due to adverse events or perceived ineffectiveness. Adverse events, particularly eye complaints, and issues with treatment effectiveness remain key concerns that need to be addressed. Additionally, variations in patient responses based on age and the temporary increase in eosinophil levels suggest the need for personalized management strategies. Overall, dupilumab has proven to be a robust option for managing moderate-to-severe atopic dermatitis, offering lasting improvements in disease control and patient satisfaction.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Frazier W, Bhardwaj NJAfp. Atopic dermatitis: Diagnosis and Treatment. 2020; 101(10):590-8.
2. Bieber TJNrDd. Atopic dermatitis: An expanding therapeutic pipeline for a Complex Disease. 2022;21(1):21-40.

3. Bylund S, von Kobyletzki LB, Svalstedt M, Svensson ÅJAd-v. Prevalence and incidence of atopic dermatitis: A Systematic Review. 2020;100(12).
4. Mastorino L, Rosset F, Gelato F, Ortoncelli M, Cavaliere G, Quaglino P, et al. Chronic pruritus in atopic patients treated with dupilumab: Real Life Response and Related Parameters in 354 Patients. 2022;15(7): 883.
5. Miniotti M, Lazzarin G, Ortoncelli M, Mastorino L, Ribero S, Leombruni PJDT. Impact on health-related quality of life and symptoms of anxiety and depression after 32 weeks of Dupilumab treatment for Moderate-to-Severe Atopic Dermatitis. 2022;35(5):e15407.
6. Kim J, Kim BE, Leung DY, editors. Pathophysiology of atopic dermatitis: Clinical implications. Allergy and asthma proceedings; OceanSide Publications; 2019.
7. David Boothe W, Tarbox JA, Tarbox MBJMoadm, challenges. Atopic Dermatitis: Pathophysiology. 2017:21-37.
8. Kimball A, Delevry D, Yang M, Chuang C-C, Wang Z, Bégo-Le-Bagousse G, et al. Long-Term Effectiveness of Dupilumab in Patients with Atopic Dermatitis: Results up to 3 Years from the RELIEVE-AD Study. *Dermatology and Therapy*. 2023;13.
9. Beck LA, Deleuran M, Bissonnette R, de Bruin-Weller M, Galus R, Nakahara T, et al. Dupilumab Provides Acceptable Safety and Sustained Efficacy for up to 4 Years in an Open-Label Study of Adults with Moderate-to-Severe Atopic Dermatitis. *Am J Clin Dermatol*. 2022;23(3):393-408.
10. Kamata M, Tada YJJI. A literature review of real-world effectiveness and safety of Dupilumab for Atopic Dermatitis. 2021;1(3):100042.
11. Ariëns LF, van der Schaft J, Spekhorst LS, Bakker DS, Romeijn GL, Kouwenhoven TA, Kamsteeg M, Voorberg AN, Oosting AJ, de Ridder I, Sloeserwij A. Dupilumab shows long-term effectiveness in a large cohort of treatment-refractory atopic dermatitis patients in daily practice: 52-Week results from the Dutch BioDay registry. *Journal of the American Academy of Dermatology*. 2021;84(4):1000-9.
12. Jo CE, Georgakopoulos JR, Ladda M, Ighani A, Mufti A, Drucker AM, Piquet V, Yeung J. Evaluation of long-term efficacy, safety, and reasons for discontinuation of dupilumab for moderate to severe atopic dermatitis in clinical practice: A retrospective cohort study. *Journal of the American Academy of Dermatology*. 2020; 82(6):1530-2.
13. Spekhorst LS, de Graaf M, Zuithoff NP, van den Reek JM, Kamsteeg M, Boesjes CM, Romeijn GL, Loman L, Haeck I, Oosting AJ, de Boer-Brand A. Dupilumab drug survival and associated predictors in patients with moderate to severe atopic dermatitis: long-term results from the Daily practice bioday registry. *Jama Dermatology*. 2022;158(9): 1048-56.
14. Nettis E, Fabbrocini G, Ortoncelli M, Pellacani G, Argenziano G, Di Leo E, Patruno C, Stingeni L, Foti C, Rongioletti F, Macchia L. Long-term effectiveness of dupilumab up to 52 weeks in atopic dermatitis in 253 adult patients. *British Journal of Dermatology*. 2021;184(3):561-3.
15. Ortoncelli M, Macagno N, Mastorino L, Gelato F, Richiardi I, Cavaliere G, et al. Long-Term Efficacy and Safety of Dupilumab in Patients with Atopic Dermatitis: A Single-Centre Retrospective Study. 2023;10(6):153.
16. Silverberg JI, Guttman-Yassky E, Gadkari A, Kuznik A, Mallya UG, Mastey V, et al. Real-world persistence with Dupilumab among Adults with Atopic Dermatitis. 2021;126(1):40-5.
17. Dal Bello G, Maurelli M, Schena D, Girolomoni G, Gisondi PJDT. Drug survival of dupilumab compared to cyclosporin in Moderate-To-Severe Atopic Dermatitis Patients. 2020;33(6):e13979.
18. Ito M, Kamata M, Uchida H, Nagata M, Fukaya S, Hayashi K, et al. Introduction of self-injection increases compliance with dupilumab administration in adult patients with atopic dermatitis: A Single-Center Retrospective Study. 2020;1(2):91.
19. Halling A-S, Loft N, Silverberg JI, Guttman-Yassky E, Thyssen JPJotAAoD. Real-world evidence of dupilumab efficacy and risk of adverse events: A Systematic Review and Meta-Analysis. 2021;84(1): 139-47.
20. Bosma AL, de Wijs LEM, Hof MH, van Nieuwenhuizen BR, Gerbens LAA, Middelkamp-Hup MA, et al. Long-term effectiveness and safety of treatment with

dupilumab in patients with atopic dermatitis: Results of the TREAT NL (TREATment of ATopic eczema, the

Netherlands) registry. Journal of the American Academy of Dermatology. 2020; 83(5):1375-84.

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