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# *Long-Term Use of Dupilumab in Atopic Dermatitis*

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***Abstract:*** Dupilumab, a fully human monoclonal antibody targeting IL-4Rα, has shown significant efficacy in the treatment of moderate to severe atopic dermatitis (AD). However, comprehensive analysis of its long-term use remains limited. This review evaluates the long-term efficacy, safety and treatment strategies of dupilumab to help clinicians develop personalised treatment plans for AD patients. Long-term studies and real-world evidence show that dupilumab maintains its therapeutic effect for up to five years, with most patients achieving sustained remission. The safety profile is generally favourable, with most adverse events being mild or moderate and reversible. As treatment duration increases, extending the dosing interval becomes an effective management strategy, particularly in patients with well-controlled disease. This approach improves patient compliance, reduces treatment costs and maintains efficacy. Based on current evidence, it is recommended to initially extend the dosing interval to every 3-4 weeks.

## 1. Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease characterized by impaired skin barrier function, inflammation, and intense pruritus.[1] AD not only severely affects the quality of life of patients but also tends to persist throughout their lives.[2] The complex pathogenesis of AD primarily involves Th2-mediated immune responses, resulting in increased levels of cytokines such as IL-4, IL-13, and IL-31. These cytokines contribute to skin barrier damage and promote the production of IgE antibodies, thereby exacerbating the inflammatory response.[3]

Targeted therapies addressing key cytokines and their signaling pathways have emerged as a new strategy in the treatment of AD. Dupilumab, a fully human monoclonal antibody, targets IL-4Rα, blocking the shared receptor component of IL-4 and IL-13, effectively inhibiting type 2 inflammation.[4] Since its approval by the U.S. FDA on March 28, 2017, as the first biologic for the treatment of moderate-to-severe AD in adults, dupilumab has demonstrated significant efficacy and safety in clinical trials. Subsequently, in June 2020, the drug was also approved for use in China. Multiple clinical trials and real-world studies have confirmed the safety and effectiveness of dupilumab.[5,6]

However, there is a lack of comprehensive analysis and evaluation of its long-term application. This review aims to provide an in-depth analysis of the long-term efficacy and safety of dupilumab,

helping clinicians develop more personalized treatment plans for AD patients.

## 2. Mechanism of Dupilumab in Atopic Dermatitis

Dupilumab is a fully human monoclonal antibody targeting the IL-4Rα, which therapeutically dually inhibits the signaling of IL-4 and IL-13 by specifically binding to type 1 and type 2 receptors.[7] Type 1 receptor complexes, composed of IL-4Rα and the common γ-chain subunit, are widely distributed in immune cells such as B cells, T cells, monocytes, eosinophils, and fibroblasts.[8] In contrast, type 2 receptor complexes, constituted by IL-4Rα and IL-13Rα1 subunits, are primarily expressed in monocytes, fibroblasts, eosinophils, activated B cells, and epithelial cells. [9,10] IL-4 can bind to both type 1 and type 2 receptors, whereas IL-13 specifically binds to type 2 receptors. [11]By binding to the IL-4Rα subunit shared by both receptors, dupilumab effectively terminates the downstream signaling of IL-4 and IL-13, thereby reducing type 2 inflammatory responses.[12] Specifically, dupilumab reduces the production of key inflammatory mediators such as IL-5 and eotaxin-3, decreases IgE-mediated allergic reactions, and modulates eosinophil function, thereby inhibiting type 2 inflammation and effectively improving the symptoms of atopic dermatitis.[5]

Studies have shown that during an average 2.5-year treatment period with dupilumab, IgE levels in AD patients steadily decrease, with this effect remaining consistent regardless of the dosing interval.[13] This underscores the sustained efficacy of dupilumab and its stable immunomodulatory effects in the long-term management of AD. Immunological studies on extended dosing intervals show that even when the dosing interval is increased from every 2 weeks (Q2W) to every 4 weeks (Q4W), no detectable IL-4Rα expression occurs, regardless of the time elapsed since the last dose.[14] These findings provide a theoretical basis for extending the dosing interval, offering patients more flexible treatment options while maintaining sustained efficacy and improving adherence.

## 3. Long-term Efficacy of Dupilumab

Long-term follow-up studies of dupilumab in patients with moderate-to-severe atopic dermatitis (AD) have reported the longest follow-up duration to date of 5 years. The LIBERTY AD open-label extension study, a 5-year international, multicenter trial involving 550 research centers across 28 countries, included adult patients with moderate-to-severe AD. At 260 weeks, 67.5% (220 of 326) of patients achieved an Investigator Global Assessment (IGA) score of 0 or 1, and 88.9% (288 of 324) of patients achieved at least a 75% improvement in the Eczema Area and Severity Index (EASI-75), demonstrating the sustained efficacy of dupilumab in long-term treatment.[15] In another 5-year retrospective study of 709 patients with moderate-to-severe AD treated with dupilumab, 37.5% achieved EASI-100 (complete resolution), 90.6% achieved EASI-90 (≥90% improvement from baseline), and 96.9% achieved EASI-75.[16] Additionally, a prospective multicenter cohort study from the BioDay registry (including four academic and ten non-academic hospitals in the Netherlands) enrolled 1286 AD patients across all age groups. After 16 weeks of treatment, the mean EASI score improved significantly from baseline to 5.1 (95% CI, 4.8–5.5), further improving to 4.1 (95% CI, 3.8–4.5) at 2 years and to 2.7 (95% CI, 1.2–4.2) at 5 years. Moreover, 71.2% of patients reported a pruritus Numerical Rating Scale (NRS) score of 4 or lower at 16 weeks, which increased to 88.2% after 5 years.[17] These findings confirm the durable efficacy of dupilumab in moderate-to-severe AD and highlight its potential as a long-term treatment option, especially for patients requiring extended disease management.

In the 1-year open-label extension (OLE) study, LIBERTY AD PED-OLE (NCT02612454), the efficacy and safety of dupilumab were evaluated in 142 children aged 6 months to 5 years with moderate-to-severe AD inadequately controlled by topical treatments. Among the participants, 60 children completed 52 weeks of treatment. By week 52, 36.2% of children achieved an IGA score of

0/1, and 96.6%, 79.3%, and 58.6% of children showed significant improvement with EASI-50, EASI-75, and EASI-90, respectively.[18] In a real-world retrospective study, 23 patients under 18 years old who received dupilumab for 1 year or longer achieved EASI-75 and IGA 0/1, with 60.8% achieving EASI-90.[19] These data support the long-term efficacy of dupilumab in children and adolescents with moderate-to-severe AD. However, further long-term studies are needed to confirm its durability and safety.

## 4. Long-term Safety of Dupilumab

Dupilumab demonstrates a favorable safety profile in long-term treatment. A study conducted in China on patients with moderate-to-severe AD showed that dupilumab was well tolerated over 52 weeks, with an overall adverse event (AE) rate of 14.52%. Most AEs were mild and did not require treatment discontinuation, with the most common events being ocular discomfort and injection site reactions.[20] In a study of elderly patients aged 80 and above with AD, dupilumab showed good safety. Out of 26 patients, 4 experienced AEs: 1 patient had injection site reactions, and another had gastrointestinal discomfort after several injections. These events resolved without special treatment, and no significant changes were noted in comorbidities.[21]

In a 5-year open-label extension study, 2276 patients (85.0%) experienced at least one treatment-emergent adverse event (TEAE), with common AEs including nasopharyngitis (28.9%), AD exacerbation (16.7%), and upper respiratory infections (13.6%). Serious TEAEs occurred in 10.6% of patients, with the most common being osteoarthritis, squamous cell carcinoma, and AD exacerbation. Despite a higher rate of AEs, most were mild or moderate, and the events did not significantly affect treatment continuity. [15] According to the results of the open-label extension study, the incidence of AEs associated with dupilumab was relatively high, likely due to several factors. First, prolonged treatment exposure is a key factor. As treatment duration increases, the cumulative risk of AEs also rises. While most AEs were mild or moderate, their frequency tended to increase with continued treatment. Second, the study design may have led to a higher reporting rate of AEs. As an open-label study, both patients and investigators were more attuned to potential AEs, which could result in a higher reporting rate compared to blinded studies. Additionally, most of the participants in this study had moderate-to-severe AD at baseline, which may have contributed to the higher incidence of AEs during treatment. Finally, as an immunomodulatory therapy, dupilumab works by inhibiting the IL-4 and IL-13 signaling pathways to regulate the immune system. While this mechanism is effective in treating AD, it may also lead to immune-related AEs such as conjunctivitis and nasopharyngitis. Although these reactions are relatively common, they are generally mild or moderate, and most patients are able to tolerate them without significant impact on the continuity of treatment.

In the PED-OLE study, which included 142 children aged 6 months to 5 years, 78.2% of patients (111 of 142) reported at least one TEAE, most of which were mild or moderate. The most common AEs included nasopharyngitis (19.7%), cough (15.5%), and fever (14.1%). Three patients (2.1%) had mild-to-moderate injection site reactions, which did not lead to treatment discontinuation. Serious TEAEs occurred in 6 patients (4.2%), with 9 serious events reported in 8 patients. These included conditions like enterobiasis, AD exacerbation, adenoid hypertrophy, and diabetic ketoacidosis. All serious TEAEs resolved, although diabetic ketoacidosis left sequelae. Only one serious AE (severe urticaria) led to permanent treatment discontinuation, though it resolved within 1 day.[18] These findings suggest that dupilumab is generally safe for long-term use in children and adolescents with AD, with most AEs being mild, reversible, and manageable. However, further studies are needed to confirm these results.

## 5. Reasons for Discontinuation of Dupilumab

In a prospective multicenter study, 306 out of 1286 patients (23.8%) discontinued dupilumab treatment during the 5-year treatment period, with a median treatment discontinuation time of 54.0 weeks (IQR: 28.0-110.0 weeks). The most common reason for discontinuation was adverse events (AEs), with 98 patients (7.6%) stopping treatment due to AEs, and the median time to discontinuation was 44.0 weeks (IQR: 26.3-95.5 weeks). Additionally, 218 patients (71.2%) discontinued treatment between December 2020 and 2022, a period coinciding with the introduction of other novel systemic drugs for AD, which may have been a significant factor in treatment interruption.[17] In a retrospective study, the 5-year drug survival rate for dupilumab was 74.1%. [16] Another real-world study conducted in China revealed that the most common reason for discontinuation was satisfactory control of AD. In this study, the 6-month and 1-year drug retention rates for dupilumab were 59.7% and 51.9%, respectively, both lower than international data. This discrepancy may be related to the fact that China's healthcare insurance system does not yet fully cover the costs of dupilumab treatment, making it easier for patients to reapply for insurance after discontinuation and relapse, resulting in a higher discontinuation rate.[22]

In conclusion, the reasons for discontinuation of dupilumab are multifactorial, including adverse events, treatment efficacy, economic factors, as well as the availability of new drugs and healthcare policies. Understanding these factors can help optimize treatment plans, improve patient adherence, and extend the duration of treatment efficacy.

## 6. Long-Term Treatment Strategies

As treatment duration increases, many patients with atopic dermatitis (AD) face the decision of whether to continue dupilumab therapy. Treatment costs, potential adverse effects, and impacts on quality of life often lead some patients to consider extending the dosing interval or discontinuing treatment. This is particularly prominent in patients with good clinical responses, where both patients and clinicians typically seek to reduce treatment burden or frequency while maintaining efficacy. However, despite existing studies showing significant efficacy of dupilumab in the short term, there is still a lack of unified treatment guidelines or consensus for its long-term management, especially in patients with good clinical responses.

Since 2019, the BioDay registry has implemented a patient-centered dupilumab dosing regimen. In this regimen, for patients who have been treated for at least 52 weeks and have an EASI score ≤7, the possibility of extending the dosing interval is considered. The decision to extend the dosing interval is made through shared decision-making with the patient, aiming to prolong the dosing interval while still controlling AD. If disease exacerbation or inadequate local treatment occurs, the patient returns to the previous effective dosing interval.[23] In a prospective multicenter study, 401 patients on a patient-centered regimen successfully reduced their dosing interval, with 83.3% maintaining disease remission. The majority used a dosing schedule of every 3 or 4 weeks. This approach significantly reduced treatment costs, saving approximately €3,977,033.98 for the 401 patients.[24] These findings demonstrate the feasibility of a patient-centered dupilumab dosing regimen. Further research shows that in patients with stable disease, extending the dosing interval can maintain efficacy, improve treatment adherence, and reduce costs.[25,26]

Studies also suggest that when the dosing interval is extended from every two weeks (Q2W) to every four weeks (Q4W), the expression of IL-4Rα remains undetectable, regardless of the time interval since the last injection. However, when the dosing interval transitions from every four weeks 300 mg to every six weeks 300 mg, there is a significant reduction in dupilumab binding to IL-4Rα, accompanied by changes in skin-resident T cell function.[14] These changes suggest that extending the dosing interval could have subtle effects on immune responses. These findings support the

recommendation to extend the dosing interval to every 3–4 weeks for patients with low disease activity, as dupilumab continues to effectively block IL-4Rα and the impact on T cell function is manageable.

In practice, the most common initial extended dosing schedule is every 3–4 weeks. [27,28] According to expert consensus in China, patients may maintain an every 2-week dosing regimen for long-term treatment, but in certain cases, such as when rashes and symptoms have been completely absent for over three months, dose reduction or discontinuation can be considered. A standard treatment period of 3–6 months is recommended, and after achieving an EASI90 or IGA 0/1, a gradual extension of the dosing interval to every 3–4 weeks may be attempted.[29]

Currently, the management strategy for dupilumab treatment relies largely on individualized decisions and clinical practice experience. While extending the dosing interval is considered a potential option to reduce treatment burden, its long-term efficacy and safety still need to be validated through further clinical studies. Therefore, developing clear long-term treatment management plans, defining indications for extending the dosing interval, and evaluating potential risks and benefits are crucial to optimizing treatment strategies for AD.

## 7. Future Research Directions

Firstly, we recognize that to fully understand the long-term efficacy and safety of dupilumab, further long-term follow-up studies are necessary, particularly those with ultra-long durations (>5 years). More research is needed to assess the sustained effects and potential risks of dupilumab across different age groups and AD subtypes. Secondly, the development of biomarkers is critical for personalized treatment. Biomarkers can help predict efficacy, optimize treatment plans, and minimize adverse reactions. The use of biomarkers can provide scientific evidence for extending dosing intervals or discontinuation, thus offering more precise treatment options for patients. Additionally, exploring combination therapies presents new possibilities for dupilumab's application. For example, combining it with other immunomodulators may enhance efficacy and provide new insights in managing refractory AD or biologic-related side effects, such as immune drift. In summary, future research should focus on the ultra-long-term efficacy and safety evaluation of dupilumab, the advancement of personalized treatments, and the exploration of combination therapies. These studies will help promote the widespread clinical application and precision medicine of dupilumab. We look forward to these studies providing more effective treatment options for AD patients.

## 8. Conclusion

Dupilumab has shown significant efficacy and acceptable safety in the long-term management of AD. Most adverse reactions are mild or moderate and are generally reversible. As treatment duration increases, extending dosing intervals becomes an effective management strategy, especially for patients with well-controlled disease. Extending dosing intervals not only improves patient adherence but also reduces treatment costs, while maintaining sustained efficacy. Based on current data, the recommended initial dosing interval extension is every 3–4 weeks.

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