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Original Research

Assessment of long-term safety and efficacy of Dupilumab therapy in patients with moderate-to-severe atopic dermatitis in the UAE: A real-life observational study

Waqas S. Abdulwahhab, Sham ZainAlAbdin, Noor Al-Areqi, Imene Amrane, Ahmed AlHashmi, Omar AbuRuz, Amal Akour, Rami Beiram, Salahdein Aburuz

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Abstract

Background: Atopic Dermatitis (AD) is a chronic relapsing and remitting inflammatory skin disease characterized primarily scaly, pruritic, and erythematous skin lesions, all of which can have a profound negative impact on a patient's quality of life. Dupilumab, is currently used for treating moderate-to-severe AD with promising efficacy and safety outcomes, however, limited data about long-term outcomes is available. **Objective:** To assess the long-term safety and efficacy of Dupilumab therapy, as well as the quality of life in patients with moderate-to-severe AD in the UAE. **Methods:** This retrospective observational study was conducted in Al-Qassimi and Tawam Hospitals, UAE. Patients' data were extracted from the electronic medical records. Long-term efficacy and quality of life upon Dupilumab use were assessed by multiple validated assessment tools for patients with AD (SCORAD, EASI, DLQI/CDLQI, vIGA, and Pruritus NRS). The safety of therapy was also assessed through documented adverse events. The change in the scores of the assessment tools was determined by paired t-test and repeated measures ANOVA. **Results:** This study included 96 patients with moderate-to-severe AD from two hospitals in the UAE between 2019 and 2023, who were followed-up over 36 months (3 years). Mean age was 23.7±13.8 years old and nearly half of the patients were females (52.1%, n= 50). In the study sample, AD most commonly appeared on the upper (88.5%, n= 85), lower extremities (71.3%, n= 78), and head-neck region (77.1%, n= 74). There was a significant improvement in patients' symptoms and quality of life, which was observed in SCORAD, EASI, DLQI/CDLQI, vIGA, and Pruritus-NRS scores ($p<0.001$) over three consequence years of receiving Dupilumab therapy (weeks 2,6,12,24,52,104, and 156). Dupilumab demonstrated considerable safety with few patients reporting side effects such as drowsiness, injection site reaction, flaring AD, and conjunctivitis. **Conclusion:** This study demonstrated that Dupilumab therapy was effective in the management of moderate-to-severe AD over long-term use and significantly improved patients' quality of life with an acceptable safety profile among children and adults.

Keywords: atopic dermatitis; dermatology; dupilumab; efficacy; safety; quality of life

Dr. Waqas SAAD. MD. Dermatology, Consultant Dermatology and Venerology, Head of Dermatology department, Al-Qassimi Hospital, Associate Clinical Professor, College of Medicine, Sharjah, UAE. Waqas. saad@ehs.gov.ae , wqs_saad@yahoo.com
Dr. Sham ZAINALABDIN*. BCPS, MSc. Clinical Pharmacy, Lecturer/Clinical Instructor, Pharmacology and Therapeutic Department, College of Medicine and Health Sciences, UAE University- AlAin, UAE. Sham.zain@uaeu.ac.ae
Noor ALAREQI. BSc. Pharmacy, PharmD student, Pharmacology and Therapeutic Department, College of Medicine and Health Sciences, UAE University- AlAin, UAE. 700040313@uaeu.ac.ae
Imene AMRANE. BSc. Pharmacy, PharmD student, College of Medicine and Health Sciences, UAE University- AlAin, UAE. 700039604@uaeu.ac.ae
Dr. Ahmed ALHASHMI. MD. Dermatology, Dermatologist - Medical Affairs, Tawam Hospital, AlAin, UAE. ahashem@seha.ae
Omar ABURUZ. Medicine, MD Student, College of Medicine, University of Jordan, Amman, Jordan. omarsalahaburuz@gmail.com
Dr. Amal AKOUR. PhD. Clinical Pharmacy, Pharmacology and Therapeutic Department, Associate Professor, College of Medicine and Health Sciences, UAE University- AlAin, UAE. aakour@uaeu.ac.ae
Department of Biopharmaceutics and Clinical Pharmacy, School of Pharmacy, the University of Jordan. Amman, Jordan.
Department of Biopharmaceutics and Clinical Pharmacy, School of Pharmacy, the University of Jordan. Amman, Jordan.
Dr. Rami BEIRAM. PhD. Pharmaceutical Sciences, Pharmacology and Therapeutic Department, Associate Professor, College of Medicine and Health Sciences, UAE University- AlAin, UAE. rbeiram@uaeu.ac.ae
Prof. Salahddein ABURUZ*. PhD. Clinical Pharmacy, Pharmacology and Therapeutic Department, Professor, College of Medicine and Health Sciences, UAE University- AlAin, UAE. saburuz@uaeu.ac.ae

INTRODUCTION

Atopic Dermatitis (AD), commonly referred to as Atopic Eczema, is a chronic relapsing and remitting inflammatory skin disease characterized primarily scaly, pruritic, and erythematous skin lesions, all of which can have a profound negative impact on a patient's quality of life.[1] AD is believed to be influenced by genetic, environmental, and immunologic factors that can alter the function of the immune system and skin barrier.[2]

It can affect both children and adults and can present with

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varying degrees of severity, ranging from mild, moderate to severe, ultimately leading to the loss of the skin's barrier function, thus, increasing the likelihood of bacterial infections. This in turn can significantly impair the quality of life of both patients and caregivers.

Despite the relapse and remission nature of AD, most patients can achieve clinical improvement and disease control through non-pharmacologic interventions. These interventions may include the use of emollients, implementation of environmental and occupational modifications, and proper patient education. Additionally, basic pharmacological therapies can be initiated for AD including conventional topical therapies like corticosteroids and calcineurin inhibitors. However, AD might not be sufficiently controlled in a subset of patients despite an optimized topical regimen containing a mixture of emollients, topical anti-inflammatory treatments, adjunctive techniques, and phototherapy. For such patients, systemic immunomodulatory agents are recommended.[3]

Dupilumab is a recently approved biologic agent that received United States Food and Drug Administration (FDA) approval in March 2017 for the treatment of moderate-to-severe Atopic Dermatitis (AD) in adults who have not achieved control with topical medications.[4] Primarily, it is indicated for patients who have not responded to previous treatment with conventional immunosuppressive agents, such as cyclosporine, methotrexate, mycophenolate mofetil, or azathioprine failed to treat AD.

Dupilumab is an IgG4 human monoclonal antibody that blocks Interluekin-4 receptor a (IL-4Ra) signals produced by IL-13 and IL-4., which in turn down-regulates T-Helper cell type 2 (TH2)-mediated inflammation in AD and other allergic conditions.[5]

Although Dupilumab is associated with many adverse events like conjunctivitis, injection-site reaction, headache and upper respiratory tract infection, it is proven to have a superior safety profile as compared to conventional immunosuppressive agents and may be safely used for long-term treatment of AD.[6]

While the safety and efficacy of Dupilumab have not yet been established in pediatric patients under 6 months of age, considerable improvement in efficacy, safety and quality of life were clearly established in adults and children who are 6 months and older.[7]

A recent study conducted in Dubai (UAE) shed light on the prevalence of AD as a common skin disease, with a prevalence rate of 4-5%. These findings underscore the significance of AD as a prevalent dermatological condition within the local population and highlight the importance of specialized care in managing this dermatological condition.[8]

Prior research on the use of Dupilumab therapy in the MENA region has primarily consisted of case reports or short-term observational studies that evaluated its effectiveness alongside other biologic agents for managing conditions such as Asthma, Urticaria, and Atopic Dermatitis. As such, the current study aims to address a gap in the existing literature by assessing the long-term safety and efficacy data for Dupilumab in both adults and pediatrics with moderate-to-severe AD as well as patients' quality of life in the UAE.

METHODS

Study Design and Sample Size

This multicentre retrospective observational study was carried out in patients who had received Dupilumab for moderate-to-severe Atopic Dermatitis during their follow-up appointments with dermatologists at Al-Qassimi or at Tawam hospitals in the United Arab Emirates between 2019 and 2023. The sample size was calculated by the Raosoft sample size calculator (http://www.raosoft.com/samplesize.html), considering a confidence interval of 95.0%, margin of error of 10.0%, and an estimated response distribution of 50.0%, the minimum number of patients required in this study is optimally 95.[9]

Ethical Consideration

The study has been approved by the Research Ethics Committees at Al-Qassimi Hospital in Sharjah, UAE (MOHAP/DXB-REC/ D.D.D/No.132 / 2022) and Tawam Hospital in Al-Ain, UAE (MF2058-2023-914). Since it is a retrospective observational study, the informed consent form was waived.

Subjects Selection and Procedures

Due to the minimum age requirement for Dupilumab use in the UAE, only patients aged six years or older with moderate-to-severe AD were eligible to participate in this study. Patients residing only in the UAE who received Dupilumab therapy for a minimum of 8 weeks and maintained regular follow-up appointments with their dermatologist for at least 52 weeks, regardless of whether treatment was temporarily discontinued due to improvement, were eligible for the inclusion. The initial dose of Dupilumab for adults is 600 mg (two 300 mg subcutaneous injections) given once as an initial loading dose followed by 300 mg subcutaneous injection given every other week. However, in pediatrics, the dose is mainly dependent on the age and weight of the child.[10] In pediatric patients (6-years - <18-years-old), whose weight ranges between 15 and less than 30kg, a total dose of 600 mg (two 300 mg subcutaneous injections) is given once as an initial loading dose, then 300 mg subcutaneous injection is given every 4 weeks. While in those with higher weight (i.e., 30 to less than 60kg), a total dose of 400 mg (two 200 mg subcutaneous injections) is given once as an initial loading dose, then 200 mg subcutaneous injection is given every other week. In children weighing 60kg or more, a total dose of 600 mg (two 300 mg subcutaneous injections) is given once as an initial loading dose, then 300 mg subcutaneous injection is given every other week.

Pregnant or breastfeeding women as well as patients who have received other monoclonal antibodies therapy other than Dupilumab, or those who were prescribed oral, inhaled, or systemic corticosteroids to treat conditions other than AD were excluded from this study.

The safety was assessed by identifying the most common adverse drug reactions and their incidence rate, as well as the continuation of the therapy rate. In addition, the efficacy was evaluated by validated assessment tools over 3-year follow-up after receiving Dupilumab, which are clearly illustrated in this study. Demographic data and clinical characteristics of patients

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were obtained at baseline. The suggested time intervals for the assessment were retrospectively collected as follows: Baseline, weeks 2, 6, 12, 24, 52, 104, and 156.

Assessment tools

Various assessment tools were used to evaluate the severity of AD, including the SCORAD, EASI, vIGA, DLQI/CDLQI, and Pruritus NRS. The SCORAD score, ranging from 0 to 103 points, categorizes AD as mild (score <25), moderate (score 25-50), or severe (score >50).[11] The EASI assessment measures clinical signs and lesion extent on a scale of 0 to 72 points, with scores below 7.1 indicating clear to mild disease and scores above 7.1 indicating moderate-to-severe disease.[12,13] The vIGA utilizes a five-point scale, with scores ranging from 0 (clear) to 4 (moderate-to-severe AD).[14] The DLQI//CDLQI is a 10-item questionnaire assessing the impact of skin diseases on various aspects of a patient's quality of life, with scores ranging from 0 to 30. Higher DLQI/CDLQI scores indicate a greater impairment of quality of life.[15,16] The Pruritus NRS measures itch intensity on a scale from 0 to 10, with higher scores indicating more severe and bothersome itchiness.[17] In addition, patients' medical records were reviewed for any reported adverse drug reaction related to Dupilumab use as well as the change in clinical outcomes through the assessment scales used by the dermatologist.

Statistical Analysis

Statistical analysis of the data was performed using the Statistical Package of Social Sciences (IBM SPSS- Version 26.0) software. Demographic characteristics were either described as frequencies (percentages) for gender, age categories, and side effects, or presented as mean ± standard deviation for age. The incidence of developing side effects of treatment was calculated. Paired Sample t- Test and Repeated Measures ANOVA were performed for the assessment of Dupilumab efficacy and patients' quality of life after receiving Dupilumab over the follow-up period. Confidence interval was fixed at 95.0% and p- value <0.05 was considered significant.

RESULTS

Demographic and Clinical Characteristics

Table 1 represents the demographic and clinical characteristics of the study population. A total of 96 patients included in this study, 52.0% (n= 50) were females and the average age was 23.7 (±13.8) years old. Among the total number of patients, 20.8% (n= 20) had allergy that is most probably related to food or drugs (15.6% (n= 15) and 4.2% (n=4); respectively). Majority of the affected body areas by AD were upper extremities, lower extremities, and head/neck areas with a lower extent of AD in the genitals area. Further details are illustrated in Table 1.

Table 1. Baseline Demographic and Clinical Characteristics of the Patients (n = 96)

Variables	N (%)
Age (Mean ± SD) 6 - < 18 years old ≥ 18 years old	23.7 ± 13.8 41 (42.7) 55 (57.3)
Gender Male Female	 46 (47.9) 50 (52.1)
Allergy	20 (20.8)
Type of Allergy Food Drug Both (food + drug) Animal/Dust	 15 (15.6) 4 (4.2) 1 (1.0) 2 (2.1)
Affected body areas by AD (patient may have multiple affected areas) Upper extremities Lower extremities Trunk abdomen Trunk back Head/Neck Genitals	 85 (88.5) 78 (81.3) 56 (58.3) 53 (55.2) 74 (77.1) 29 (30.2)

Assessment of Safety

A limited number of patients (26.0%, n= 25) discontinued Dupilumab therapy during the 2-year (104-week) period. These discontinuations were attributed to adverse drug reactions (ADRs) (9.4%, n= 9), switching to an alternative therapy due to inadequate effectiveness of Dupilumab for their AD (2.1%, n= 2), and discontinuation of therapy due to complete remission of AD in a subset of the population (14.6%, n= 14).

Out of the 96 patients who received Dupilumab therapy, a total of 17 (17.7%) patients experienced at least one of the reported 7 adverse drug reactions. The most common adverse events reported by patients were injection site reaction (5.2%, n= 5), drowsiness (3.1%, n= 3), conjunctivitis (4.2%, n= 4), flaring AD (2.1%, n= 2) of the patients. Other reported adverse drug reactions were at 1.0% (n= 1) incidence rate, such as herpes simplex virus infection (HSV), vitiligo, and punctal stenosis (narrowing/occlusion of lacrimal duct). Only 9.4% (n= 9) of the patients had to discontinue Dupilumab therapy due to intolerable adverse events such as injection-site reaction (ISR), drowsiness, flaring AD, conjunctivitis, punctal stenosis, and vitiligo over 1 year of receiving Dupilumab therapy. Further details about the incidence of ADRs after receiving and discontinuing Dupilumab therapy are presented in Table 2.

Table 2. Incidence of Adverse drug reactions after receiving Dupilumab therapy and discontinuation of the treatment (n= 96)

ADRs	n (%)	Discontinuation of treatment n (%)	Continued treatment n (%)
Drowsiness	3 (3.1)	1 (1.0) at week 6	2 (2.1)
ISR	5 (5.2)	4 (4.2) at week 6	1 (1.0)
HSV	1 (1.0)	-	1 (1.0)
Flaring AD	2 (2.1)	1 (1.0) at week 60	1 (1.0)
Punctal Stenosis	1 (1.0)	1 (1.0) at week 95	-
Vitiligo	1 (1.0)	1 (1.0) at week 60	-
Conjunctivitis	4 (4.2)	1 (1.0) at week 60	3 (3.1)
Total (n out of 96)	**17(17.7)**	**9 (9.4)**	**8 (8.3)**

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Almost more than two-thirds of the patients were still receiving Dupilumab therapy (74.0%, n= 71/96); of which 58.3% (n= 56/96) of the patients have completed up to 3 years Dupilumab therapy, while the rest have completed Dupilumab therapy for a maximum of 1 year (15.6%, n= 15/96). It is worth mentioning that all study patients were followed-up by their dermatologists for a period of three years, regardless of their treatment status. Moreover, there was no significant impact of neither age nor gender on the incidence of ADRs.

Assessment of Efficacy and Patients' Quality of Life

The average scores for each SCORAD, EASI, vIGA, DLQI/CDLQI, and Pruritus NRS have significantly improved over 3 years follow-up compared to the baseline average scores (p <0.001). Moreover, the average scores of all the above-mentioned assessment tools have significantly improved between each time intervals up to year 2 (p <0.001), while it remained steady thereafter (p > 0.05). Table 3 represents the average scores of the assessment tools used by the dermatologists to assess the efficacy of Dupilumab and the patients' quality of life.

Figure 1 highlights the percentage of improvement in the extent and severity of AD using the SCORAD score over 3 years follow-up after receiving Dupilumab. SCORAD average Score has improved significantly from baseline throughout the follow-up period (3 years) (p <0.001). Around 28.8% improvement in SCORAD was observed after 2 weeks of Dupilumab compared to baseline (p <0.001), while 93.3% improvement in SCORAD was observed after 1-year of receiving Dupilumab compared to baseline (p <0.001). After that, the average SCORAD peaked around 97.0% at year 2 and has remained sustainable thereafter (p >0.05).

Table 3. Average score of the assessment tools for Dupilumab therapy over the follow-up period (3 years)

Assessment Tool	Time interval (Week #)							
	Baseline n= 96	**Week 2 n= 96**	**Week 6 n= 91**	**Week 12 n= 91**	**Week 24 n= 91**	**Week 52 (year 1) n= 91**	**Week 104 (year 2) n= 71**	**Week 156 (year 3) n= 56**
SCORAD (Mean ± SD)	53.0 ± 10.3	37.7 ± 11.1	25.5 ± 10.1	15.6 ± 8.9	8.8 ± 7.8	3.4 ± 8.5	1.3 ± 4.8	1.1 ± 4.0
P- Value (compared to baseline)	-	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***
EASI (Mean ± SD)	50.3 ± 18.0	34.2 ± 15.8	22.3 ± 12.8	14.0 ± 10.2	7.5 ± 6.7	2.0 ± 4.8	0.8 ± 2.4	0.6 ± 2.0
P- Value (compared to baseline)	-	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***
vIGA (Mean ± SD)	4.0 ± 0.1	3.0 ± 0.3	2.3 ± 0.6	1.6 ± 0.7	1.1 ± 0.8	0.4 ± 0.8	0.2 ± 0.5	0.2 ± 0.5
P- Value (compared to baseline)	-	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***
DLQI (Mean ± SD)	28.7 ± 3.1	17.4 ± 5.1	10.5 ± 4.5	6.2 ± 3.5	3.4 ±2.6	1.2 ±2.7	0.5 ± 1.3	0.4 ±1.2
P- Value (compared to baseline)	-	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***
CDLQI (Mean ± SD)	28.4 ± 2.6	17.8 ± 5.1	11.0 ± 5.0	6.6 ± 3.8	3.7 ±2.6	1.4 ± 2.4	0.8 ± 1.9	0.8 ± 1.9
P- Value (compared to baseline)	-	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***
Pruritus- NRS (Mean ± SD)	9.8 ± 0.6	6.0 ±1.3	4.0 ± 1.7	2.4 ± 1.7	1.3 ± 1.6	0.7 ± 1.6	0.3 ± 0.8	0.3 ± 0.8
P- Value (compared to baseline)	-	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***

*P- value < 0.05 is considered significant.

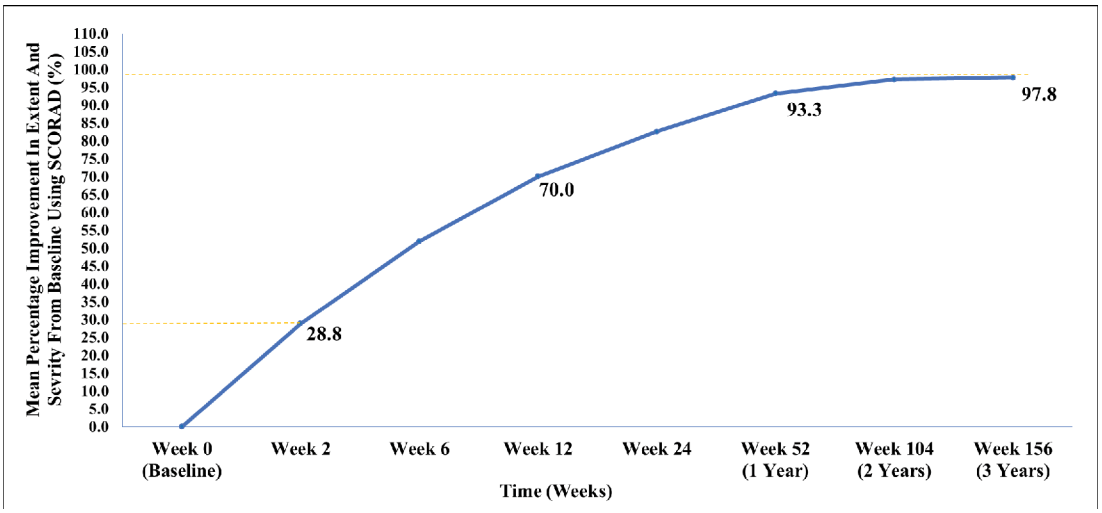

Figure 1. Improvement in SCORAD score after Dupilumab therapy over 3 years

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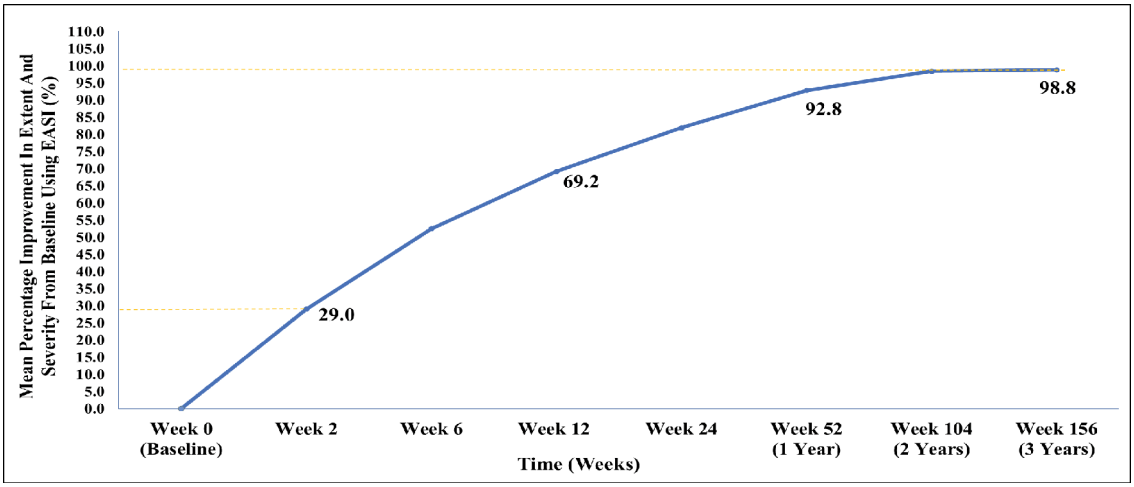

Figure 2. Improvement in EASI score after Dupilumab therapy over 3 years

The percentage of improvement in the extent and severity of AD using the EASI score over 3 years follow-up after receiving Dupilumab is presented in Figure 2. EASI average Score has improved significantly from baseline throughout the follow-up period (3 years) ($p < 0.001$). At week 2, the EASI score has improved by 29.0% compared to baseline ($p < 0.001$) and achieved almost 93.0% at year 1. Consequently, the EASI score has improved and remained stable at round 98.5% between year 2 and 3.

The vIGA average Score has improved significantly from baseline throughout the follow-up period (3 years) ($p < 0.001$). The average vIGA score showed a 25.0% improvement of AD severity at week 2 and has dramatically achieved 90.0% improvement at year 1. Later, the vIGA score has peaked at 95.0% between year 2 and 3 steadily as illustrated in Figure 3.

Figure 4 shows two curves, the percentage of improvement in patients' quality of life using the DLQI score for adults (≥ 18 years old) and the CDLQI for children (6-to-17-year-old) over 3 years follow-up after receiving Dupilumab. The DLQI and CDLQI have improved by 40.0% and 36.8%; respectively at week 2 and have reached almost 96.0% and 95.0% at year 1; respectively. After that, around 99.0% and 97.0% were achieved for each DLQI and CDLQI scores at year 2 and remained consistent thereafter ($p > 0.05$).

Pruritus NRS average Score has improved significantly from baseline throughout the follow-up period (3 years) ($p < 0.001$). The average score improved by almost 39.0% at weeks 2, then sharply increased by 93.0% compared to baseline average score. Later, the average score peaked around 98.0% at year 2 and steadily improved thereafter as displayed in Figure 5.

Stratified data analysis indicated no remarkable impact of age or gender on the severity of the disease or quality of life outcomes.

DISCUSSION

This multicentre retrospective observational study included 96 patients with moderate to severe Atopic Dermatitis (AD). The study is the first in MENA region to assess the long-term safety and efficacy of Dupilumab therapy as well as patients' quality of life at two centres in the UAE. Our findings revealed that age and gender did not significantly impact the occurrence of adverse drug reactions, since the total number of patients who developed each ADR was too small. Our results demonstrated that Dupilumab has effectively improved disease severity, as evaluated by SCORAD, EASI, vIGA, Pruritus NRS and DLQI/CDLQI scores. Notably, significant improvements were observed as early as week 2 of treatment, and these positive trends continued with even greater improvement by week 52 compared to baseline scores, then remained sustained after year 2 of follow-up. The effectiveness of the treatment was consistent across various demographic groups, indicating that age and gender did not significantly impact the response to therapy. Furthermore, the distribution of age categories and gender within the study group was relatively even, ensuring a balanced representation of different age ranges and both genders.

Among the 96 patients receiving Dupilumab primarily for AD, eight patients were undergoing Dupilumab treatment for concomitant inflammatory conditions. This utilization of Dupilumab can be attributed to its mechanism of action, which has demonstrated efficacy in managing various inflammatory conditions such as Prurigo Nodularis[18], Asthma[19], Nasal polyposi[20], and steroid-induced rosacea.[21]

Interestingly, most patients exhibited good tolerance to Dupilumab with an acceptable safety profile. These findings emphasize the potential of Dupilumab as an effective and safe treatment option for the management of moderate-to-severe AD in real-life clinical practice.

In our study, 17.7% of our patients reported having an adverse event, with each patient reporting a single event. These events encompassed a range of 7 different adverse reactions. While some patients exhibited tolerability towards these adverse events, others experienced intolerable effects, necessitating the discontinuation of treatment in 9 individuals, comprising 9.4% of our study population. In a long-term study, a mere 4.3% had discontinued treatment due to treatment-emergent

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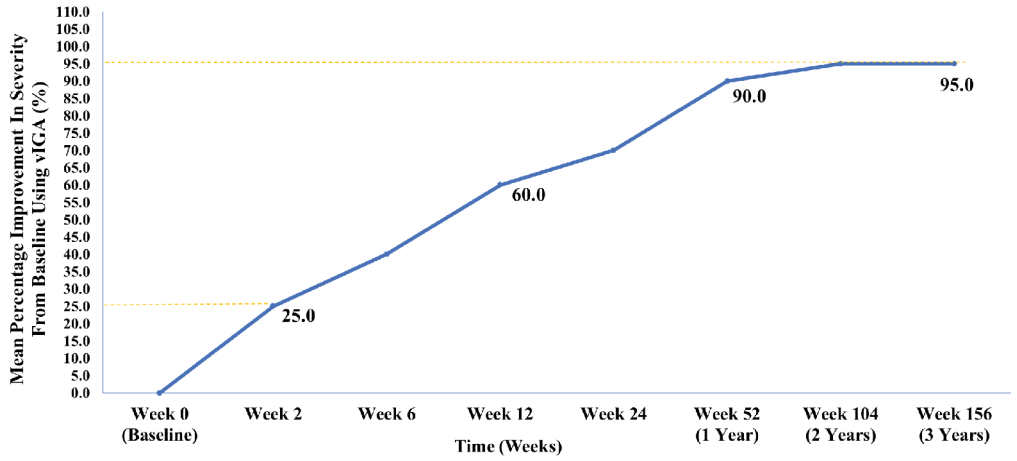

Figure 3. Improvement in vIGA score after Dupilumab therapy over 3 years

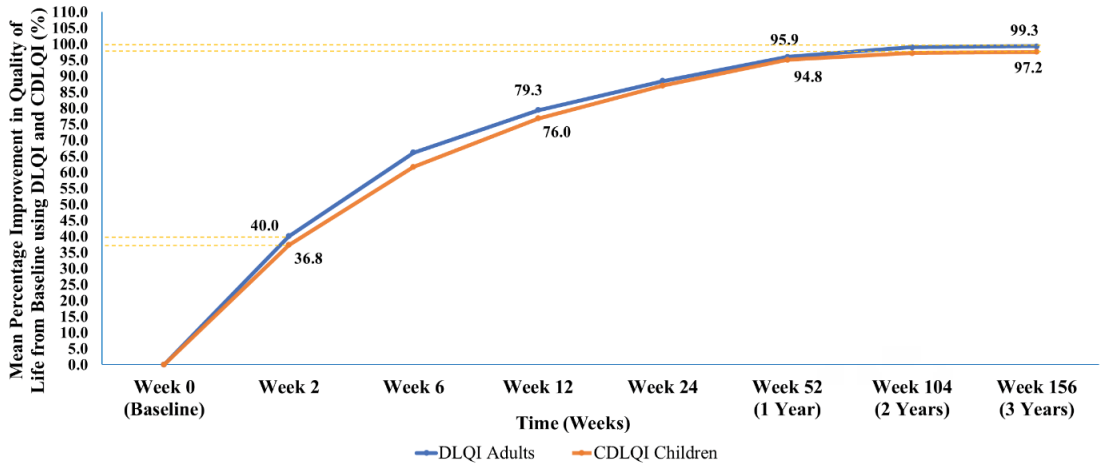

Figure 4. Improvement in DLQI and CDLQI scores after Dupilumab therapy over 3 years

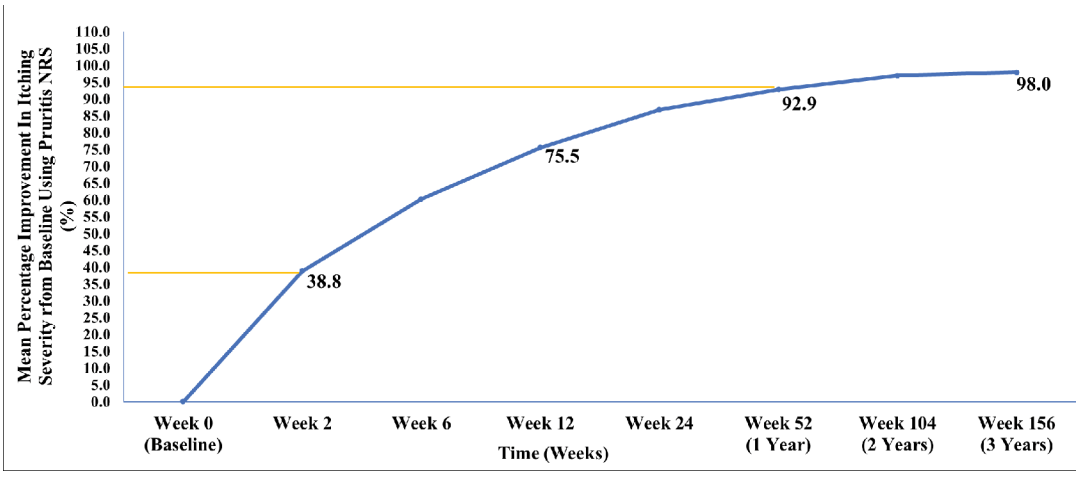

Figure 5. Improvement in Pruritus NRS score after D upilumab therapy over 3 years

adverse events. This disparity in findings may be attributed to the substantial difference in the study design and number of participants between our study and the aforementioned interventional study compared to our observational study.[22]

Given the nature of Dupilumab as a subcutaneously administered biologic, it is anticipated to elicit an injection-site reaction.[23] In our study, injection-site reactions emerged as the predominant adverse event presented by five patients upon receiving Dupilumab injections and exhibiting an incidence

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of 5.2%. This occurrence is considered lower than the rate observed in clinical trials, which stood at 13.2%.[24] Aligned with our findings, similar incidences of injection-site reactions ranging from 2.6% to 9.2% were reported in real-life studies conducted in China, Italy, Japan, and France.[25-28] In our study, one patient encountered a transient injection-site reaction that was resolved after the application of topical steroids. However, the remaining four patients discontinued treatment due to the persistent nature of the reaction that led to unwillingness to continue therapy. It is noteworthy that some patients experienced this adverse event either immediately after the first injection or within the initial weeks of treatment.

Four patients, representing 4.2% of our study population, developed conjunctivitis, which is less than the reported occurrence of approximately 8.0% in clinical trials.[24] Real-life studies conducted in China, Italy, South Korea, The United Kingdom, and France have reported a range of conjunctivitis occurrences varying from 2.6% to 38.2%.[25,29-31,28] The lower incidence of conjunctivitis observed in our study may be attributed to the preventive prescription of lubricant and artificial tear drops.[32] Out of the four patients who developed conjunctivitis, one presented with severe bilateral conjunctivitis, necessitating the discontinuation of Dupilumab therapy. The other patients' conjunctivitis was managed by the ophthalmologist, allowing them to continue their Dupilumab therapy without interruption.

A total of three patients, constituting 3.1% of the study population, exhibited symptoms of dizziness/drowsiness subsequent to the injection. Notably, all of these occurrences were documented among individuals falling within the age range of 18-20 years. However, due to the small number of patients who developed this side effect, it is hard to consider this finding significant. Of these patients, two were able to endure this adverse event until complete remission of their AD was achieved and therapy was discontinued accordingly. Conversely, the third patient experienced intolerable dizziness and opted for immediate discontinuation of the treatment. A multicentre study in Colombia revealed that around 2.2% of their population had a sensation of dizziness lasting up to 72 hours following the injection administration.[33] In another study that was conducted in Canada, dizziness was reported as one of the generalized nonspecific symptoms with an incidence of 2.8%.[34]

It is noteworthy that while this adverse event has been recognized as a potential rare occurrence,[35] it lacks sufficient documentation in post-marketing surveillance studies and the limited number of patients in our study prevents us from determining whether the observed adverse event is linked to the drug itself or patient-related factors.

One patient, accounting for 1% of the study population, reported recurrent oral herpes simplex, for which the patient received both oral and topical antiviral treatment. These results align with real-life studies conducted in Italy, China, and the United States, which reported occurrences ranging from 0.9% to 2.6%.[25,26.36] slightly lower than the incidence observed in clinical trials at 6.1%.[24] In a study conducted in The United Kingdom, it was observed that orofacial herpes simplex occurred in 8.4% of the patients, where half of these individuals were concurrently utilizing systemic immunosuppressants, which could potentially contribute to the elevated incidence of this adverse event.[37]

While clinical trials have shown a lower incidence of AD flaring or exacerbations in Dupilumab compared to the placebo group,[24] it is important to note that Dupilumab as a therapy can also potentially cause AD exacerbations as an adverse event. Two of the patients, constituting approximately 2.1%, encountered episodes of AD flares while undergoing Dupilumab treatment. These findings align with the results of retrospective studies conducted in Canada and The United States where the incidence of flares was 1.9% and 3.9% respectively.[38,36] In a recent Colombian study, a notable decrease in the number of patients encountering flares was observed following the initiation of Dupilumab treatment compared to the pre-treatment period. However, among the patients who had not previously reported any flares prior to receiving Dupilumab, only a single patient (1.1%) reported two episodes of AD flare following treatment initiation, which is consistent with the findings of our study.[33]

Vitiligo was identified as a rare adverse event in our study, occurring in a single patient and accounting for 1% of the study population. Consequently, Dupilumab therapy was discontinued, and the patient underwent phototherapy treatment to address vitiligo. Upon follow-up, the patient achieved complete remission of AD with no relapse for more than a year after Dupilumab discontinuation. This can be either a drug-related adverse event or maybe as a consequence of AD progression, where patients with AD are at high risk of developing other autoimmune diseases such as vitiligo or alopecia areata.[39,40] Very few case reports were published associating vitiligo with Dupilumab therapy. In a documented case report from Japan, a patient developed vitiligo and underwent vitiligo therapy while concurrently receiving Dupilumab treatment, but no improvement was observed. Eventually, economic constraints necessitated the discontinuation of Dupilumab therapy by the patient. During the follow-up period, slight re-pigmentation was observed after the cessation of Dupilumab; however, there was no reduction in the size of the affected area.[41] In another case report from Italy, vitiligo had also developed while receiving Dupilumab therapy, and the decision was made to initiate vitiligo treatment while continuing Dupilumab therapy, aiming to maintain AD complete clinical response. Remarkably, this approach led to the complete remission of both AD and vitiligo.[42]

One of the patients reported unilateral irritation, blurred vision and tearing in the right eye within the first few months of therapy and was referred to an ophthalmologist. After confirming the diagnosis of punctal stenosis, a joined decision of discontinuing therapy was made between the patient's dermatologist and ophthalmologist after a total of 22 months of Dupilumab therapy.[43] After discontinuation of dupilumab, signs and symptoms of punctal stenosis had resolved completely without any surgical intervention. With regards to AD, the patient demonstrated prior improvement while receiving Dupilumab, and this improvement has persisted even

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after discontinuing Dupilumab therapy. In a recent 2021 case series, three patients undergoing Dupilumab therapy for AD experienced epiphora and conjunctivitis. Upon examination, all three patients were diagnosed with punctal stenosis, with one patient progressing to punctal obstruction. Despite attempting various strategies to address the condition, discontinuation of Dupilumab was necessary for two out of the three patients due to the severity of the stenosis and the limited success of the interventions. However, the third patient achieved symptom resolution and remained asymptomatic for six weeks following successful surgical interventions such as probing, punctoplasty, and silicone intubation.[44]

The same patient who developed punctal stenosis, had also developed signs of migraine within a year of treatment and later on was diagnosed with Multiple Sclerosis by a neurologist with an early manifestation of migraine. The diagnosis of Multiple Sclerosis was made three years after the first Dupilumab injection and one year after therapy discontinuation. This is currently being investigated by the dermatologist and the neurologist to determine any potential factors that may have contributed to its occurrence, and to ascertain whether this is associated with Dupilumab therapy or other underlying causes.

It is important to note that these adverse events should be evaluated in the context of the overall benefit-risk profile of Dupilumab in the management of moderate-to-severe AD. The incidence, severity and tolerability of these adverse events may vary among patients, and appropriate management strategies should be implemented to minimize their impact and ensure safe and effective treatment.

The use of Dupilumab therapy over a period of 3 years demonstrated substantial improvement in the SCORAD scores. Within 2 weeks, the percentage of improvement was 28.8%, increasing to 93.3% after 1 year, and remaining sustainable throughout the study duration. These findings align with a Chinese study that assessed Dupilumab's efficacy using the SCORAD index, in which there was almost an improvement by 30% at week 2 and around 53% improvement by week 16.[25] Additionally, a French multicentre study reported a 50% improvement in SCORAD after 3 months of therapy in 52.8% of their study population , further substantiating the effectiveness of Dupilumab in real-life scenarios.[28]

Evaluation of the EASI scores revealed a similar trend in the improvement achieved with Dupilumab therapy over 3 years. The percentage of improvement was approximately 29% after 2 weeks and reached 92.8% after 1 year, remaining sustainable throughout the study period. In contrast, a Colombian study reported an improvement of 75% in the EASI score after 1 year of therapy, which was comparatively lower than the improvement percentage obtained in our study after 1 year of therapy.[33] Similarly, an Indian study demonstrated significant improvement, with approximately 68% of patients achieving a 75% reduction in EASI scores following 6 months of Dupilumab treatment.[45]

The use of Dupilumab therapy resulted in notable improvement in the vIGA scores over 3 years. Within 2 weeks, the percentage of improvement was around 25.0%, increasing to 90.0% after 1 year, and remaining sustainable thereafter. A real-world study assessing Dupilumab efficacy reported that more than 70% of their patients with IGA score ≥ 3 improved to an IGA score of ≤ 2 at the 4th month after Dupilumab initiation, including 42.8% of patients of have achieved IGA score of 0/1.[46]

Dupilumab therapy demonstrated substantial improvement in both DLQI and CDLQI scores over a 3-year period. After 2 weeks, the percentage of improvement was approximately 40.0% for DLQI and 36.8% for CDLQI, which respectively increased to around 96.0% and 95.0% after 1 year and remained consistent. An Italian multicentre study showed that at week 16 of therapy, 93.0% of their patients achieved a 4-point or higher improvement in DLQI compared to baseline after 16 weeks of therapy, which is consistent with our findings.[29]

Our findings are consistent as well with those of a separate study conducted in pediatric patients, which demonstrated a significant decrease in CDLQI scores. At baseline, the patients had an average CDLQI score of 13.53 ± 2.88 which was significantly improved to 1.60 ± 0.63 after 6 months of standardized treatment protocol. These findings further reaffirm the efficacy of Dupilumab in both children and adults with moderate-to-severe AD.[47]

Dupilumab therapy resulted in a significant improvement in the Pruritus NRS scores over 3 years. Within 2 weeks, the percentage of improvement was approximately 39.0%, increasing to nearly 93.0% after 1 year, and remaining sustainable thereafter. These findings are consistent with those of a real-world study, wherein a substantial 70.5% of patients exhibited a decrease of ≥ 3 points in Pruritus NRS scores from pre- to post-index at month 4, irrespective of age, sex, or clinical characteristics, including treatment history.[46]

This study has several notable strengths as it represents the first multicentre investigation in the MENA region to provide comprehensive data on the long-term safety and efficacy of Dupilumab, along with an assessment of the quality of life in patients with moderate-to-severe AD. Additionally, this study evaluates the efficacy of Dupilumab and patients' quality of life by comparing baseline measurements to improvement of the symptoms and quality of life at each time interval over 3 years follow-up. These findings emphasize that Dupilumab is a potent therapeutic intervention for alleviating symptoms associated with moderate to severe AD. Furthermore, the study offers detailed insights into adverse drug reactions, including their incidence rate and discontinuation of the medication. It also discusses how these adverse reactions were managed and tolerated by patients. However, it is important to note that this study is based on retrospective data, which introduces the possibility of bias and loss of control in terms of patients' follow-up.

Additionally, the sample size in this study was convenient for analysis purposes, although no additional patients were included beyond the two sites as the drug's approval was in 2017. It is important to acknowledge that the absence of patients below 6 years old in this study is attributed to the restrictions by the Ministry of Health and Prevention in the UAE on the use of Dupilumab for this age group until its recent approval in 2023. Insufficient data regarding this specific age category precluded its inclusion in our study.

CONCLUSION

The current study presents real-world evidence on the long-term efficacy and safety of Dupilumab therapy in patients with moderate-to-severe Atopic Dermatitis over a three-year follow-up. Our findings demonstrate substantial and sustained improvements in disease severity, as indicated by various measurement scales, along with a positive impact on patients' quality of life throughout the treatment. Dupilumab exhibited minimal side effects, predominantly encompassing injection site reactions, drowsiness, and conjunctivitis. Interestingly, no major adverse events were reported beyond the second year of treatment. Moreover, the analysis of gender and age did not reveal any significant differences in treatment outcomes, suggesting that the response to therapy was not significantly influenced by age or gender.

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CONFLICTS OF INTEREST STATEMENT

The authors declared no conflicts of interest.

ETHICAL CONCERNS

The present study has obtained approval from both Al-Qassimi and Tawam hospitals in the UAE, where the study has been conducted.

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CONTRIBUTOR ROLES TAXONOMY

Abdulwahhab W: Conceptualization, Investigation, patients' follow-up, review & editing; ZainAlabdin S**:** Conceptualization, Methodology, Data curation, Formal Analysis, Investigation, Writing – review & editing; Al-Areqi N: Data collection, Data curation, Writing – original draft, review & editing; Amrane I: Data collection, Data curation, Writing – original draft, review & editing**;** AlHashmi A: Investigation, patients' follow-up, review & editing; AbuRuz O: Data curation, Methodology, review & editing**;** Akour A: Data curation, Methodology, Statistical Analysis consultation, review & editing; Beiram R: Data curation, Methodology, review & editing; AbuRuz S**:** Supervision, Methodology, Data curation, Statistical analysis consultation, review & editing.

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