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ORIGINAL RESEARCH

Longitudinal Response Trajectories with Dupilumab or Upadacitinib in Moderate-to-Severe Atopic Dermatitis: A Multicentre Real-World Study: IL-AD (Italian Landscape Atopic Dermatitis)

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ABSTRACT

Introduction: Understanding how treatment responses evolve over time is essential for optimising therapeutic strategies in moderate-to-severe atopic dermatitis (AD). While clinical trials have demonstrated the efficacy of targeted therapies, real-world evidence describing longitudinal response trajectories remains limited. This study aimed to characterise temporal patterns of

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clinical response in patients with AD treated with dupilumab or upadacitinib in routine clinical practice.

***Methods*:** A multicentre real-world observational study was conducted using data from the Italian AD-Landscape platform, a structured clinical database collecting longitudinal information on patients receiving advanced systemic therapies for AD. Adult patients initiating dupilumab or upadacitinib between July 2019 and January 2026 were included if baseline and at least week-4 assessments were available. Disease severity and patient-reported outcomes were evaluated using the Eczema Area and Severity Index (EASI), Investigator's Global Assessment (IGA), Pruritus Numerical Rating Scale (P-NRS) and Sleep Numerical Rating Scale (S-NRS) at baseline and at weeks 4, 16, 36 and 52. Categorical response thresholds (EASI75, EASI90 and EASI100) and safety outcomes were analysed descriptively.

***Results*:** A total of 2625 patients were included (dupilumab *n*=2085; upadacitinib *n*=540). Both treatments produced rapid and sustained improvements in clinician-reported and patient-reported outcomes throughout the 52-week follow-up. Mean EASI scores decreased from 25.6 ± 6.5 to 2.2 ± 2.9 in the dupilumab group and from 19.1 ± 9.2 to 2.9 ± 5.7 in the upadacitinib group at week 52, respectively. Upadacitinib demonstrated faster early response kinetics, whereas dupilumab showed a progressive accumulation of clinical benefit over time, resulting in convergence of response rates during long-term follow-up. Safety findings were consistent with known mechanism-specific profiles.

***Conclusions*:** In this large real-world cohort, both dupilumab and upadacitinib provided substantial and sustained clinical improvements in moderate-to-severe AD. Distinct response kinetics were observed, with faster early responses with upadacitinib and progressively increasing responses with dupilumab, supporting a personalised approach to treatment selection in routine clinical practice.

Keywords: Atopic dermatitis; Treatment; Dupilumab; Upadacitinib; Clinical response trajectories

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Key Summary Points

Why carry out this study?

Real-world evidence describing how treatment responses evolve over time in patients with moderate-to-severe atopic dermatitis (AD) receiving advanced therapies remains limited.

Understanding longitudinal response trajectories is clinically relevant because therapies with different mechanisms of action may show distinct response kinetics.

This study aimed to evaluate longitudinal clinical response trajectories in patients with moderate-to-severe AD treated with dupilumab or upadacitinib in routine clinical practice.

What was learned from the study?

In a large real-world cohort of 2625 patients, both dupilumab and upadacitinib produced rapid and sustained improvements in disease severity, pruritus, sleep impairment, and quality of life over 52 weeks.

Upadacitinib showed faster early response kinetics, whereas dupilumab demonstrated a progressive accumulation of clinical benefit over time.

These findings highlight the importance of evaluating treatment trajectories rather than isolated timepoints and may help inform personalised therapeutic decision-making in routine clinical practice.

INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease characterised by intense pruritus, eczematous lesions, sleep disturbance and a substantial impairment of quality of life [1, 2]. Affecting up to 10–20% of children and approximately 2–8% of adults worldwide, AD represents one of the most prevalent inflammatory skin disorders and poses a significant long-term burden for both patients and healthcare systems [1, 2]. Furthermore, AD is increasingly recognised as a systemic disease associated with multiple atopic comorbidities, including asthma, allergic rhinitis and conjunctivitis, reflecting the complex interplay between epidermal barrier dysfunction, immune dysregulation and environmental factors [1, 2]. The pathogenesis of AD is driven predominantly by type 2 immune inflammation, characterised by overexpression of interleukin (IL)-4, IL-13 and related cytokine pathways, together with additional contributions from Janus kinase (JAK)-dependent signalling cascades involved in pruritus, inflammation and barrier impairment [3, 4]. Recent advances in the understanding of AD pathogenesis have led to a therapeutic revolution over the past years, with the introduction of targeted systemic therapies that have significantly improved disease control compared with conventional immunosuppressive agents [5]. Among currently available advanced therapies, dupilumab, a monoclonal antibody targeting the IL-4 receptor α subunit and inhibiting IL-4 and IL-13 signalling, represents the first biologic approved for moderate-to-severe AD and has demonstrated sustained efficacy and a favourable safety profile in both clinical trials and real-world studies [6–8]. More recently, oral JAK inhibitors, including upadacitinib, have emerged as highly effective therapeutic options capable of rapidly suppressing multiple inflammatory pathways simultaneously through intracellular signal modulation [9–11]. In detail, upadacitinib selectively inhibits JAK1 signalling and has shown rapid improvements in disease severity, pruritus, and patient-reported outcomes in phase III clinical trials, often characterised by a rapid onset of action [9–11]. Despite the efficacy reported in clinical trials, translating these results into routine clinical practice remains challenging. Indeed, patients enrolled in clinical trials are highly selected and often do not reflect the clinical complexity encountered in daily dermatological practice, where treatment decisions are influenced by disease phenotype, prior therapeutic exposure, comorbidities, difficult-to-treat anatomical areas, and patient preferences. Consequently, real-world evidence (RWE) has

become increasingly important to complement clinical trial data by providing insights into treatment effectiveness, safety, and persistence under everyday clinical conditions.

An emerging area of interest in AD research concerns the understanding of longitudinal response trajectories, since evaluating how clinical improvement evolves over time provides insights that extend beyond traditional cross-sectional efficacy endpoints [12]. Traditional comparative analyses focussing solely on response rates at predefined timepoints may fail to capture clinically relevant aspects of treatment dynamics, such as speed of response, durability of improvement, and cumulative clinical benefit over time [12]. These temporal patterns are especially relevant when comparing therapies with distinct mechanisms of action, as biologics and small molecules may exhibit different response kinetics despite achieving comparable long-term outcomes. Understanding these temporal patterns may therefore support more personalised treatment selection, optimise therapeutic sequencing, and better align treatment expectations between physicians and patients in routine clinical practice.

Currently, evidence describing treatment trajectories in patients with AD is limited, particularly in large real-world populations. The aim of the present study was to characterise longitudinal clinical response trajectories in adult patients with moderate-to-severe AD treated with dupilumab or upadacitinib in routine clinical practice using data derived from the Italian AD-Landscape platform.

METHODS

A multicentre observational real-world study was conducted using data extracted from the AD-Landscape platform, a structured clinical database designed to collect routinely recorded information on patients with AD treated with advanced systemic therapies in daily clinical practice. The platform prospectively collects anonymised demographic, clinical, therapeutic and follow-up data entered by participating centres during routine visits, allowing for longitudinal monitoring of treatment outcomes in real-life settings. Data entry within the AD-Landscape platform follows standardised data collection procedures and predefined clinical variables, ensuring consistency across participating centres and improving data completeness and reliability compared with traditional retrospective chart reviews. The use of standardised outcome measures routinely adopted in clinical practice allows for the generation of high-quality real-world evidence reflecting treatment effectiveness and safety under everyday clinical conditions while preserving external validity. The present study was designed as a retrospective cohort analysis using prospectively collected real-world data, with the primary aim of describing longitudinal clinical response trajectories over time in patients treated with dupilumab or upadacitinib.

Adult patients aged ≥18 years with a confirmed diagnosis of moderate-to-severe AD who initiated treatment with either dupilumab or upadacitinib between July 2019 and January 2026 within the AD-Landscape platform were eligible for inclusion. Baseline was defined as the visit corresponding to treatment initiation. Patients were included if at least baseline and week 4 disease severity assessment was available. Individuals with missing treatment initiation data or insufficient clinical information preventing outcome evaluation were excluded. The progressive reduction in the number of evaluable patients across follow-up visits reflects the real-world nature of the AD-Landscape registry. Differences in available sample size at each timepoint may be related to variable follow-up duration, missed scheduled visits, treatment discontinuation or loss to follow-up. Therefore, effectiveness outcomes were calculated using evaluable patients at each visit. Treatment selection and management followed routine clinical practice and national prescribing indications, with therapeutic decisions made independently by treating physicians. In routine clinical practice within the AD-Landscape platform, no predefined wash-out periods were systematically required before initiating dupilumab or upadacitinib, and treatment initiation followed national prescribing indications and physician judgment. Concomitant

systemic immunosuppressive therapies were not administered during treatment with these advanced agents. However, the use of topical therapies, including topical corticosteroids or emollients, may have occurred as part of routine clinical management but was not systematically recorded within the registry database.

Baseline demographic and clinical variables recorded in the AD-Landscape platform included age, sex, body mass index, age at disease onset, clinical phenotype of AD and the presence of atopic comorbidities. Disease severity was assessed using validated outcome measures routinely collected in clinical practice, including the Eczema Area and Severity Index (EASI), Investigator's Global Assessment (IGA), Pruritus Numerical Rating Scale (P-NRS) and Sleep Numerical Rating Scale (S-NRS). Assessments were recorded at baseline and at follow-up visits scheduled according to routine care, corresponding to weeks 4, 16, 36, and 52.

Treatment effectiveness was evaluated both as longitudinal changes in continuous severity scores and as categorical clinical responses defined by achievement of EASI75, EASI90, and EASI100 at each follow-up visit. Safety outcomes included adverse events (AEs) occurring during treatment and treatment discontinuations, with reasons for discontinuation recorded whenever available. Of note, dyslipidaemia was recorded as an AE only when newly detected during treatment in patients without previously documented dyslipidaemia at baseline. Lipid abnormalities were identified according to routine laboratory assessments and clinical documentation in the medical record during follow-up visits.

Given the real-world nature of data collection within the AD-Landscape platform, missing follow-up assessments were anticipated; therefore, response rates were calculated using evaluable patients at each timepoint. Data included in the AD-Landscape platform are anonymised prior to analysis.

This work is a retrospective analysis conducted exclusively on fully anonymized clinical data, with no possibility of identifying individual patients and without any intervention or modification of clinical practice. According to Italian national regulations, including the provisions of the Italian Data Protection Authority (Garante per la Protezione dei Dati Personali), in particular General Authorisation No. 9/2016 and its subsequent alignment with the EU General Data Protection Regulation (EU Regulation 2016/679, GDPR), anonymized data are not considered personal data, and their use for research purposes does not require ethical committee approval. This regulatory interpretation is consistent with major international ethical frameworks, including the Declaration of Helsinki (2013, Article 32) and ICH-GCP E6(R2), which specify that ethical review is not required when research is conducted on pre-existing, fully anonymized data.

Statistical Analysis

Continuous variables were expressed as mean and standard deviation (SD), while categorical variables were reported as absolute numbers and percentages. Baseline characteristics between treatment groups were compared using Student's *t*-test or the Mann–Whitney *U* test for continuous variables and the chi-squared or Fisher's exact test for categorical variables, as appropriate. Clinical effectiveness outcomes were analysed descriptively across follow-up visits at weeks 4, 16, 36, and 52. Predefined subgroup analyses were performed within the upadacitinib-treated population to explore potential differences in treatment response according to prior dupilumab exposure (dupilumab-naïve versus dupilumab-experienced patients) and according to upadacitinib dosage (15 mg versus 30 mg). Because clinically relevant baseline differences in disease severity were observed between treatment groups, particularly in baseline EASI scores, categorical response outcomes were primarily presented descriptively rather than as formal comparative efficacy analyses to minimise bias related to baseline imbalance and treatment allocation in real-world practice. Therefore, between-group comparisons should be interpreted as descriptive and exploratory rather than inferential. Response rates were calculated using evaluable patients at each visit. Safety outcomes, including AEs and treatment discontinuations, were analysed descriptively and compared between treatment groups using

chi-squared or Fisher's exact tests when appropriate. Formal statistical comparisons were avoided when event counts were low and statistical power was insufficient. All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant.

RESULTS

After application of the predefined inclusion criteria and selection of patients treated with dupilumab or upadacitinib with available baseline and follow-up assessments, 2625 patients were included in the final analysis. Among them, 2085 patients received dupilumab and 540 patients received upadacitinib. Baseline demographic and clinical features of study populations have been summarized in Table 1 and Table 2.

Overall, male individuals accounted for 50.7% (n = 1058) of patients treated with dupilumab and 52.2% (n = 282) of those treated with upadacitinib. Mean age was 43.1 ± 22.4 years in the dupilumab group and 39.7 ± 16.1 years in the upadacitinib group (p = 0.006). The mean age at AD onset was 22.2 ± 25.6 years and 19.2 ± 21.5 years, respectively (p < 0.001). Mean body mass index was comparable between groups, though slightly higher in upadacitinib cohort (23.7 ± 4.2 versus 24.4 ± 4.1 kg/m^2).

Clinical phenotype distribution differed significantly between treatment groups (overall p < 0.001), likely reflecting treatment allocation patterns in routine clinical practice (Table 1). Classical AD represented the most frequent clinical presentation, observed in 70.8% (n = 1476) of dupilumab-treated patients and 82.6% (n=446) of upadacitinib-treated patients. Prurigo phenotype was more commonly observed in the dupilumab cohort (12.8% versus 2.4%), whereas palmo-plantar eczema was more frequent among patients receiving upadacitinib (3.5% versus 0.8%). Other phenotypes included generalised eczema (5.8% versus 3.3%), generalised lichenoid eczema (5.1% versus 1.5%), nummular eczema (3.4% versus 4.3%) and erythroderma (1.1% in both groups). Less frequent variants such as portrait dermatitis, psoriasiform eczema and head/neck eczema were observed only in a small proportion of patients (Table 1). Atopic comorbidities were common across the study population. Allergic rhinitis was present in 44.6% (n = 929) of dupilumab-treated patients compared with 33.5% (n = 181) of those receiving upadacitinib (p < 0.001). Conjunctivitis was reported in 33.2% versus 24.8% (p < 0.001), while asthma was observed in 28.4% versus 21.7%, respectively (p < 0.005) (Table 1).

A substantial proportion of patients had received previous systemic therapies prior to treatment initiation (Table 1). Oral corticosteroids had been used in 52.7% (n = 1100) of dupilumab-treated patients compared with 21.1% (n = 114) in the upadacitinib group. Previous cyclosporine exposure was frequent in both cohorts (47.7% versus 48.9%). Phototherapy had been administered in 4.8% versus 3.0% of patients.

Exposure to other advanced therapies differed between groups. Prior dupilumab use was recorded in 45.2% (n = 244) of patients initiating upadacitinib, whereas previous upadacitinib exposure before dupilumab was uncommon (0.8%). Previous treatment with tralokinumab (1.1% versus 6.7%), methotrexate (1.0% versus 4.4%), baricitinib (0.5% versus 1.5%), and abrocitinib (0.2% versus 2.2%) was also documented.

Longitudinal changes in clinician-reported and patient-reported outcomes are summarised in Table 2. Both treatment groups showed rapid and sustained improvements across all evaluated measures, including EASI, Pruritus Numerical Rating Scale (P-NRS) and Sleep Numerical Rating Scale (S-NRS).

In the dupilumab group, mean EASI scores decreased from 25.6 ± 6.5 at baseline to 7.0 ± 6.2 at week 4, followed by further reductions to 3.8 ± 4.0 at week 16, 2.8 ± 3.4 at week 36 and 2.2 ± 2.9 at week 52. A comparable improvement was observed in patients treated with upadacitinib, in whom mean EASI decreased from 19.1 ± 9.2 at baseline to 5.1 ± 6.1 at week 4, 2.5 ± 4.2 at week 16, 2.1 ± 4.0 at week 36 and 2.9 ± 5.7 at week 52 (Table 2).

IGA, P-NRS and S-NRS improved substantially during treatment in both cohorts as well (Table 2). Overall, improvements in objective

Table 1 Baseline demographic and clinical features of study populations

	Dupilumab	Upadacitinib	*P**
Number of patients	2085	540	
Sex			
Male	1058 (50.7%)	282 (52.2%)	ns
Female	1027 (49.3%)	258 (47.8%)	ns
Mean age	43.1 ± 22.4	39.7 ± 16.1	0.006
Age of AD onset (years)	22.2 ± 25.6	19.2 ± 21.5	<0.001
Body mass index	23.7 ± 4.2	24.4 ± 4.1	ns
Clinical phenotype			
Classical	1476 (70.8%)	446 (82.6%)	<0.001*
Prurigo	266 (12.8%)	13 (2.4%)	
Generalised eczema	121 (5.8%)	18 (3.3%)	
Generalised lichenoid eczema	107 (5.1%)	8 (1.5%)	
Nummular eczema	70 (3.4%)	23 (4.3%)	
Erythroderma	23 (1.1%)	6 (1.1%)	
Palmo-plantar eczema	17 (0.8%)	19 (3.5%)	
Portrait dermatitis	0	4 (0.8%)	
Psoriasiform eczema	0	2 (0.4%)	
Head/neck eczema	0	1 (0.2%)	
Atopic comorbidities:			
Rhinitis	929 (44.6%)	181 (33.5%)	<0.001
Conjunctivitis	692 (33.2%)	134 (24.8%)	<0.001
Asthma	593 (28.4%)	117 (21.7%)	<0.005
Previous systemic treatments:			
Oral corticosteroids	1100 (52.7%)	114 (21.1%)	
Cyclosporine	995 (47.7%)	264 (48.9%)	
Phototherapy	99 (4.8%)	26 (3.0%)	
Tralokinumab	23 (1.1%)	36 (6.7%)	
Methotrexate	21 (1.0%)	24 (4.4%)	
Upadacitinib	16 (0.8%)	14 (2.6%)	
Dupilumab	12 (0.6%)	244 (45.2%)	
Baricitinib	10 (0.5%)	8 (1.5%)	
Abrocitinib	5 (0.2%)	12 (2.2%)	

*Clinical phenotypes were mutually exclusive. *p*-Value refers to overall chi-squared test for distribution across categories. Previous treatments are descriptive and not statistically compared due to intrinsic treatment-selection bias

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Table 2 Clinical outcomes of study populations

	Dupilumab	Upadacitinib
Baseline		
Patients	2085	540
EASI	25.6 ± 6.5	19.1 ± 9.2
IGA	3.3 ± 0.7	3.1 ± 1.0
P-NRS	8.4 ± 1.7	7.2 ± 2.4
S-NRS	6.9 ± 3.1	5.8 ± 3.1
Week 4		
Patients	2085	540
EASI	7.0 ± 6.2	5.1 ± 6.1
IGA	1.4 ± 1.0	1.2 ± 1.0
P-NRS	3.3 ± 2.4	2.2 ± 2.4
S-NRS	1.9 ± 2.4	1.3 ± 2.2
Week 16		
Patients	1555	446
EASI	3.8 ± 4.0	2.5 ± 4.2
IGA	1.0 ± 0.8	0.7 ± 0.9
P-NRS	2.5 ± 2.3	1.4 ± 2.2
S-NRS	1.1 ± 2.0	0.7 ± 1.8
Week 36		
Patients	1346	376
EASI	2.8 ± 3.4	2.1 ± 4.0
IGA	0.9 ± 0.8	0.5 ± 0.8
P-NRS	2.3 ± 2.3	1.4 ± 2.3
S-NRS	0.8 ± 1.7	0.6 ± 1.7
Week 52		
Patients	1164	304
EASI	2.2 ± 2.9	2.9 ± 5.7
IGA	0.7 ± 0.7	0.5 ± 0.8
P-NRS	2.1 ± 2.3	1.5 ± 2.1
S-NRS	0.7 ± 1.8	0.4 ± 1.4
EASI 75		
Week 4	1013/2085 (48.6%)	299/540 (55.4%)
Week 16	1204/1555 (77.4%)	346/446 (77.6%)
Week 36	1166/1346 (86.6%)	305/376 (81.1%)
Week 52	1062/1164 (91.2%)	256/304 (84.2%)
EASI 90		
Week 4	573/2085 (27.5%)	168/540 (31.1%)
Week 16	738/1555 (47.5%)	262/446 (58.7%)
Week 36	828/1346 (61.5%)	241/376 (64.1%)
Week 52	813/1164 (69.8%)	213/304 (70.1%)
EASI 100		
Week 4	335/2085 (16.1%)	134/540 (24.8%)
Week 16	309/1555 (19.9%)	209/446 (46.9%)
Week 36	370/1346 (27.5%)	195/376 (51.9%)
Week 52	418/1164 (35.9%)	177/304 (58.2%)

Due to significant baseline EASI differences between groups, EASI response rates are presented descriptively and not statistically compared. Percentages are calculated on evaluable patients at each visit.

EASI Eczema Area and Severity Index, *IGA* Investigator's Global Assessment, *P-NRS* Pruritus Numerical Rating Scale, *S-NRS* Sleep Numerical Rating Scale

disease severity, symptom burden and sleep impairment were already evident during the first weeks of therapy and were progressively maintained throughout follow-up, demonstrating sustained multidimensional disease control (Table 2).

The primary objective of the study was to evaluate longitudinal clinical response trajectories. The proportions of patients achieving EASI75, EASI90 and EASI100 progressively increased throughout follow-up in both treatment groups, demonstrating cumulative clinical benefit over time (Table 2, Fig. 1).

At week 4, EASI75 was achieved by 48.6% (1013/2085) of dupilumab-treated patients and 55.4% (299/540) of upadacitinib-treated patients. Response rates increased markedly by week 16, reaching 77.4% (1204/1555) and 77.6% (346/446), respectively. Continued improvement

was observed at week 36 (86.6% versus 81.1%) and week 52 (91.2% versus 84.2%) (Table 2, Fig. 1a).

Higher response thresholds followed a similar trajectory. EASI90 responses increased from 27.5% versus 31.1% at week 4 to 47.5% versus 58.7% at week 16, reaching 61.5% versus 64.1% at week 36 and 69.8% versus 70.1% at week 52 (Table 2, Fig. 1b).

Complete skin clearance (EASI100) progressively increased over time, from 16.1% versus 24.8% at week 4 to substantially higher rates during long-term follow-up, confirming sustained accumulation of treatment benefit (Table 2, Fig. 1c). Overall, response curves showed rapid early improvement followed by progressive consolidation of clinical response, with the steepest increase occurring between week 4 and week 16 and subsequent stabilisation through week 52. These findings highlight distinct response kinetics characterised by a faster onset of action with upadacitinib and a progressively accumulating clinical benefit with dupilumab. Indeed, higher proportions of patients treated with upadacitinib achieved EASI75, EASI90 and EASI100 during the initial follow-up visits, indicating a faster onset of clinical response. However, response rates in the dupilumab group progressively increased over time, resulting in a partial convergence of response rates at later timepoints, particularly for EASI75 and EASI90, although numerical differences remained for the most stringent endpoint (EASI100).

Of interest, given the substantial proportion of patients initiating upadacitinib after prior exposure to dupilumab, a subgroup analysis was performed within the upadacitinib cohort according to previous dupilumab treatment (Table 3). At baseline, disease severity was significantly higher in dupilumab-naïve patients compared with dupilumab-experienced individuals (mean EASI 20.8 ± 8.8 versus 17.2 ± 9.2, $p < 0.001$). Despite this baseline difference, both subgroups demonstrated rapid and sustained clinical improvement during follow-up, with progressive reductions in EASI scores observed from week 4 through week 52. However, dupilumab-naïve patients consistently achieved higher response rates across all evaluated timepoints. At week 4, EASI75 was achieved by 57.1% of dupilumab-naïve patients compared with 53.3% of dupilumab-experienced patients, increasing to 79.9% versus 74.8% at week 16, 84.7% versus 77.2% at week 36 and 87.9% versus 80.3% at week 52. A similar pattern was observed for higher response thresholds: EASI90 responses were 31.9% versus 30.3% at week 4, 61.1% versus 55.9% at week 16, 69.4% versus 58.3% at week 36 and 75.2% versus 64.6% at week 52, while complete skin clearance (EASI100) was achieved by 27.7% versus 21.3% at week 4, 48.0% versus 44.4% at week 16, 54.6% versus 48.9% at week 36 and 61.1% versus 55.1% at week 52 in dupilumab-naïve and dupilumab-experienced patients, respectively. Globally, although clinical improvement was observed in both subgroups, prior dupilumab exposure was associated with numerically lower response rates throughout follow-up, suggesting that treatment history may influence the magnitude of response to upadacitinib in real-world clinical practice.

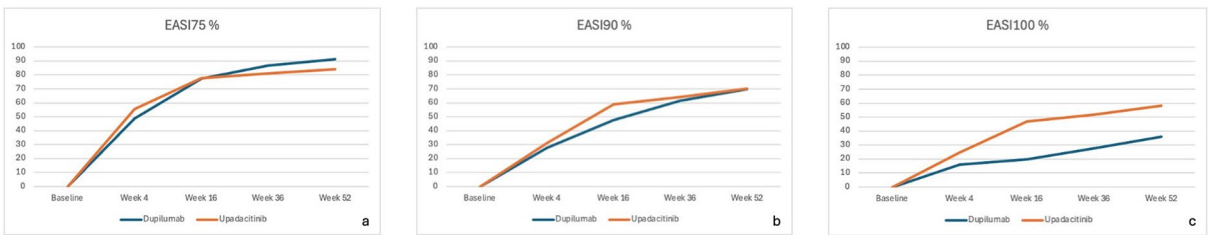

Fig. 1 Longitudinal EASI75 (**a**), EASI90 (**b**) and EASI100 (**c**) response rates in patients with atopic dermatitis treated with dupilumab or upadacitinib. Percentages were calculated on evaluable patients at each timepoint: baseline (dupilumab n=2085; upadacitinib n = 540), week 4 (n = 2085; n = 540), week 16 (n = 1555; n = 446), week 36 (n = 1346; n = 376) and week 52 (n = 1164; n = 304). *EASI* Eczema Area and Severity Index

Subanalysis of Clinical Outcomes of Study Populations Receiving Upadacitinib by Treatment Dosage

A subgroup analysis was performed according to upadacitinib dosage. At baseline, 392 patients received upadacitinib 15 mg and 148 patients received upadacitinib 30 mg, with comparable disease severity between groups (mean EASI 19.3 ± 9.0 versus 18.9 ± 9.5, respectively). Both dosage groups showed a rapid and sustained clinical improvement, with marked reductions in mean EASI scores already evident at week 4 and maintained throughout follow-up (all $p < 0.001$ versus baseline). Mean EASI decreased from 19.3 ± 9.0 at baseline to 5.1 ± 6.0, 2.5 ± 4.0, 1.9 ± 3.4 and 1.6 ± 3.8 at weeks 4, 16, 36 and 52 in the 15-mg group, and from 18.9 ± 9.5 to 5.2 ± 6.5, 2.7 ± 4.9, 2.9 ± 5.6 and 3.0 ± 5.3 in the 30-mg group, respectively. Clinical response rates were largely comparable between doses. At week 4, EASI75 was achieved by 220/392 patients (56.1%) receiving 15 mg and 79/148 (53.4%) receiving 30 mg, while EASI90 and EASI100 responses were observed in 121/392 (30.9%) versus 47/148 (31.8%) and 99/392 (25.3%) versus 35/148 (23.6%), respectively. Similar results were observed at week 16 (EASI75: 77.3% versus 78.5%; EASI90: 57.5% versus 62.6%; EASI100: 46.8% versus 46.7%). During longer follow-up, response rates remained high in both groups, with numerically higher sustained responses in the 15-mg cohort at week 36 and week 52 (EASI75 at week 52: 86.9% versus 75.0%; EASI90: 71.2% versus 66.2%; EASI100: 57.2% versus 55.9%), although these findings should be interpreted descriptively given the observational design and dose adjustments occurring during follow-up. Data are summarized in Table 4.

Overall, 492/540 patients (91.1%) did not show any recorded dose modification between consecutive timepoints, maintaining the same upadacitinib dosage throughout the available follow-up visits. A total of 48/540 patients (8.9%) experienced at least one dose modification during follow-up. At the individual patient level, dose escalation from 15 mg to 30 mg was observed in 20/540 patients (3.7%), while dose reduction from 30 mg to 15 mg occurred

Table 3 Longitudinal effectiveness of upadacitinib in dupilumab-experienced versus dupilumab-naïve patients

	Dupilumab-experienced	Dupilumab-naïve
Baseline		
Patients	244	296
EASI	17.2 ± 9.2	20.8 ± 8.8
Week 4		
Patients	244	296
EASI	4.5 ± 5.7	5.6 ± 6.5
Week 16		
Patients	202	244
EASI	2.5 ± 4.0	2.5 ± 4.4
Week 36		
Patients	180	196
EASI	2.2 ± 3.7	2.1 ± 4.3
Week 52		
Patients	147	157
EASI	2.0 ± 4.4	1.8 ± 4.1
EASI 75		
Week 4	130/244 (53.3%)	169/296 (57.1%)
Week 16	151/202 (74.8%)	195/244 (79.9%)
Week 36	139/180 (77.2%)	166/196 (84.7%)
Week 52	118/147 (80.3%)	138/157 (87.9%)
EASI 90		
Week 4	74/244 (30.3%)	94/296 (31.9%)
Week 16	113/202 (55.9%)	149/244 (61.1%)
Week 36	105/180 (58.3%)	136/196 (69.4%)
Week 52	95/147 (64.6%)	118/157 (75.2%)

Table 3 continued

	Dupilumab-experienced	Dupilumab-naïve
EASI 100		
Week 4	52/244 (21.3%)	82/296 (27.7%)
Week 16	92/202 (45.5%)	117/244 (48.0%)
Week 36	88/180 (48.9%)	107/196 (54.6%)
Week 52	81/147 (55.1%)	96/157 (61.1%)

Due to significant baseline EASI differences between groups, EASI response rates are presented descriptively and not statistically compared. Percentages are calculated on evaluable patients at each visit.

EASI Eczema Area and Severity Index

in 20/540 patients (3.7%). Bidirectional dose modifications, defined as adjustments occurring in both directions at different timepoints, were identified in 8/540 patients (1.5%). Dose modifications occurred predominantly during early–intermediate follow-up, with 11/48 modifications (22.9%) between baseline and week 4, 17/48 (35.4%) between week 4 and week 16, 16/48 (33.3%) between week 16 and week 36 and 4/48 (8.3%) between week 36 and week 52.

Reasons for dose modification were available for 36/540 patients (6.7%). Overall, lack of efficacy, including both primary and secondary inefficacy, represented the most frequent cause (14/36, 38.9%). Other non-safety-related reasons, including clinical remission or clinical worsening, accounted for 7/36 cases (19.4%), whereas adverse events collectively accounted for 15/36 cases (41.7%).

Treatment Persistence and Safety

Safety outcomes observed during follow-up are summarised in Table 5. Overall, both treatments demonstrated favourable safety profiles consistent with previously reported clinical trial and real-world evidence, and no unexpected safety signals were identified during the observation period.

A total of 216 (10.4%) and 205 (38.0%) AEs were reported in patients receiving dupilumab and upadacitinib, respectively ($p < 0.001$). Of note, individual patients could experience more than one AE. Most AEs were mild to moderate in severity and did not require treatment discontinuation.

In the dupilumab group, the most frequently reported AEs included ocular manifestations, particularly conjunctivitis and ocular discomfort, occurring in 100 (4.8%) patients.

Among patients receiving upadacitinib, the most commonly observed AE was dyslipidaemia ($n = 92$, 17.0%), followed by CPK elevation ($n = 38$, 7.0%) and acneiform eruptions ($n = 22$, 4.1%).

Treatment discontinuation due to AEs was infrequent overall, at 39 (1.9%) versus 13 (2.4%), respectively. Overall, the distribution of AEs reflected the known mechanism-specific safety profiles of the two therapies, with predominantly ocular events observed during dupilumab treatment and mainly dermatologic or haematological events reported with upadacitinib, consistent with previous clinical trials and real-world studies. Of note, the higher incidence of AEs observed with upadacitinib should be interpreted in light of routine laboratory monitoring, which may increase detection of asymptomatic laboratory abnormalities. Treatment persistence over the observation period remained high in both treatment groups, reflecting sustained treatment effectiveness and overall tolerability in a real-world setting. In addition to dose modifications, treatment discontinuations were also evaluated. Treatment was discontinued in 134 patients (6.4%) receiving dupilumab and 36 patients (6.7%) treated with upadacitinib. Discontinuations occurred for both medical and non-medical reasons. In the dupilumab group, the most frequent causes of treatment interruption included lack or loss of efficacy (47 patients; 2.3%) followed by AEs (39 patients; 1.9%). Similarly, among patients receiving upadacitinib, treatment discontinuation was primarily related to lack or loss of efficacy (14 patients; 2.6%) and AEs (13 patients; 2.4%). Overall, discontinuation rates, summarised in Table 6, were low throughout follow-up, and most treatment interruptions were attributable to known safety

Table 4 Subanalysis of clinical outcomes of study populations receiving upadacitinib by treatment dosage

	Upadacitinib 15 mg	Upadacitinib 30 mg
Number of patients	392	148
Baseline		
Baseline	19.3 ± 9.0	18.9 ± 9.5
Week 4	5.1 ± 6.0	5.2 ± 6.5
Week 16	2.5 ± 4.0	2.7 ± 4.9
Week 36	1.9 ± 3.4	2.9 ± 5.6
Week 52	1.6 ± 3.8	3.0 ± 5.3
Number of patients		
Baseline	392	148
Week 4	392	148
Week 16	339	107
Week 36	292	84
Week 52	236	68
EASI 75		
Week 4	220/392 (56.1%)	79/148 (53.4%)
Week 16	262/339 (77.3%)	84/107 (78.5%)
Week 36	239/292 (81.8%)	66/84 (78.6%)
Week 52	205/236 (86.9%)	51/68 (75.0%)
EASI 90		
Week 4	121/392 (30.9%)	47/148 (31.8%)
Week 16	195/339 (57.5%)	67/107 (62.6%)
Week 36	186/292 (63.7%)	55/84 (65.5%)
Week 52	168/236 (71.2%)	45/68 (66.2%)
EASI 100		
Week 4	99/392 (25.3%)	35/148 (23.6%)
Week 16	159/339 (46.8%)	50/107 (46.7%)
Week 36	150/292 (51.4%)	45/84 (53.6%)
Week 52	135/236 (57.2%)	38/68 (55.9%)

EASI Eczema Area and Severity Index

or effectiveness considerations rather than unexpected clinical issues.

DISCUSSION

The present multicentre real-world study represents one of the largest longitudinal real-world evaluations of treatment response trajectories in adult patients with moderate-to-severe AD receiving dupilumab or upadacitinib in routine clinical practice. Going beyond static scores, this study focusses on the temporal dynamics of response, providing clinically meaningful information on onset of action, cumulative benefit, depth of response and duration over a 52-week period. Globally, both therapies induced rapid and sustained improvements across clinician-reported (EASI, IGA) and patient-reported outcomes (P-NRS, S-NRS), confirming their effectiveness in a real-world population characterised by substantial prior treatment exposure and phenotypic heterogeneity. However, distinct response kinetics emerged. Upadacitinib demonstrated a more rapid onset of action, with numerically higher proportions of patients achieving EASI75, EASI90 and EASI100 at week 4. Conversely, dupilumab showed a progressive and cumulative trajectory, with steady increases in response rates over time and leading to convergence of categorical response rates at long-term follow-up. These findings mirror the mechanistic differences between extracellular IL-4/IL-13 receptor blockade and intracellular JAK1 inhibition. Importantly, treatment allocation reflected differences in baseline characteristics. Patients receiving upadacitinib had a

Table 5 Summary of adverse events observed during the study period

Adverse event	Dupilumab *n* (%)	Upadacitinib *n* (%)
Total	216/2085 (10.4%)	205/540 (38.0%)
Conjunctivitis	100 (4.8%)	0
CPK elevation	0	38 (7.0%)
Acneiform reaction	0	22 (4.1%)
Herpes zoster	0	11 (2.0%)
Nausea	0	6 (1.1%)
Red face	20 (1.0%)	0
Herpes simplex	7 (0.3%)	11 (2.0%)
COVID	6 (0.3%)	0
Upper respiratory tract infection	5 (0.2%)	7 (1.3%)
Dyslipidaemia	5 (0.2%)	92 (17.0%)
Injection site reaction	4 (0.2%)	Not applicable
Transaminase elevation	0	5 (0.9%)
Folliculitis	0	5 (0.9%)
Other	56 (2.7%)	4 (0.7%)

Adverse events occurring only once during the observation period were grouped under the category "others" to ensure clarity and readability of the safety analysis.

significantly lower baseline EASI compared with those treated with dupilumab, likely reflecting real-world prescribing patterns rather than lower disease complexity. Notably, patients initiating upadacitinib had more frequent exposure to previous biologic therapies and were often characterised by clinically challenging disease presentations, including involvement of sensitive or functionally relevant anatomical areas. These features may not be fully captured by global severity scores such as EASI, which may partly explain the apparent discrepancy between

Table 6 Summary of treatment discontinuations observed during the study period

Reason for discontinuation	Dupilumab *n* (%)	Upadacitinib *n* (%)
Total	134/2085 (6.4%)	36/540 (6.7%)
Loss of efficacy	47 (2.3%)	14 (2.6%)
Transfer	18 (0.9%)	3 (0.6%)
Adverse drug reaction (overall)	39 (1.9%)	13 (2.4%)
Clinical remission	2 (0.1%)	2 (0.4%)
Lost to follow-up	24 (1.2%)	2 (0.4%)
Pregnancy	4 (0.2%)	2 (0.4%)

clinical complexity and baseline EASI values observed between treatment groups.

Indeed, nearly half of the upadacitinib cohort had prior dupilumab exposure, whereas dupilumab was more frequently prescribed in biologic-naïve patients. Of note, biologic-naïve individuals receiving dupilumab achieved numerically higher response rates across follow-up, suggesting that earlier use of targeted therapy may be associated with enhanced clinical outcomes. These findings are consistent with recent real-world evidence evaluating long-term upadacitinib outcomes according to prior systemic therapy exposure. In a study with follow-up up to 96 weeks, systemic-therapy-naïve patients tended to achieve higher response rates compared with previously treated individuals, suggesting that treatment history may influence therapeutic outcomes in routine clinical practice. Similarly, in our cohort, patients naïve to dupilumab achieved numerically higher response rates during upadacitinib treatment compared with dupilumab-experienced patients, further supporting the potential impact of prior biologic exposure on treatment effectiveness [21]. Regarding upadacitinib dosage, more than 90% of patients maintained stable dosing during follow-up, and dose adjustments were infrequent. These findings suggest that most patients achieve adequate control with the standard approved dose, reserving escalation for selected cases of insufficient response. Safety findings were consistent with known mechanism-specific profiles. Dupilumab was primarily associated with ocular events, particularly conjunctivitis, whereas upadacitinib was more frequently linked to dyslipidaemia, CPK elevation, acneiform eruptions and viral infections. Globally, treatment discontinuation due to adverse events was low and comparable between groups.

Compared with existing literature [13–22], the present study contributes additional real-world evidence by describing longitudinal response trajectories in a large multicentre cohort of patients treated with dupilumab or upadacitinib over 52 weeks. Few real-world studies have explored cumulative response trajectories or examined how early differences in response kinetics evolve over time in routine clinical practice. Demonstrating initial divergence followed by long-term convergence, our findings support a trajectory-based framework for interpreting therapeutic response.

From a clinical perspective, these results highlight the importance of tailoring treatment choice to individual patient needs. When rapid symptom control is required, particularly in patients with severe itch, sleep impairment or significant impact on daily activities, the faster onset of upadacitinib may represent an advantage. Further, dupilumab offers a progressive and sustained improvement over time, supported by robust long-term safety data, which may make it preferable in patients with relevant comorbidities or when long-term treatment stability is a priority. Rather than positioning these agents as competitors, our findings support a personalised approach on the basis of disease characteristics, prior treatments and patient expectations.

Strengths and Limitations

The present study has several strengths that should be considered when interpreting the findings. First, the analysis was conducted using data derived from the AD-Landscape platform, a large multicentre real-world database collecting prospectively recorded clinical information from routine clinical practice. The large sample size and inclusion of patients managed under everyday clinical conditions enhance the external validity of the results and allow for a reliable evaluation of treatment response trajectories beyond the controlled environment of randomized clinical trials. In addition, the use of harmonised and routinely collected outcome measures, including EASI, IGA, P-NRS and S-NRS, enabled a comprehensive longitudinal assessment of both objective disease severity and patient-reported outcomes over a 52-week follow-up period. Another important strength lies in the study focus on longitudinal response kinetics rather than direct comparative effectiveness. By describing temporal response trajectories, this analysis provides clinically relevant information on the speed and durability of treatment response, aspects that are often underrepresented in traditional efficacy comparisons

but highly relevant for treatment decision-making in real-world practice. Nevertheless, several limitations must be acknowledged. First, the observational and non-randomised design introduces the possibility of confounding by indication and channelling bias. Furthermore, no multivariable-adjusted analyses or propensity-score-based methods were applied to account for potential confounding factors. Therefore, differences observed between treatment groups may partly reflect baseline imbalances, including disease severity and prior biologic exposure, and comparative interpretations should be considered descriptive rather than causal. Although regression-based adjustment or propensity score approaches may partially address baseline imbalances, such methods cannot fully eliminate channelling bias inherent to treatment allocation in real-world clinical practice. Future studies using adjusted analytical frameworks may further explore comparative effectiveness between therapies in more homogeneous patient populations. Treatment allocation was determined by routine clinical practice rather than randomisation, resulting in baseline differences between groups, including disease severity and previous exposure to advanced therapies. In particular, patients treated with upadacitinib showed a higher rate of prior biologic exposure, which may reflect greater clinical complexity not fully captured by global severity scores such as EASI. It should be noted that certain clinical phenotypes such as palmo-plantar eczema may be less accurately captured by global severity scores such as EASI, although the proportion of patients with this phenotype in our cohort was very small. Second, although data collection within the AD-Landscape platform follows standardised procedures, missing follow-up assessments are inherent to real-world studies. Response rates were therefore calculated using evaluable patients at each timepoint, which may introduce attrition-related bias and potentially influence the interpretation of longitudinal response trajectories over time. However, this approach reflects routine clinical practice and avoids assumptions related to imputation methods. Third, AEs were recorded according to routine clinical documentation rather than systematic protocol-driven monitoring, potentially leading to underreporting of mild events. Moreover, the relatively short minimum follow-up requirement (week 4) used as an inclusion criterion may introduce heterogeneity in longitudinal follow-up when interpreting long-term response trajectories. Finally, the descriptive analytical approach adopted for categorical response outcomes was intentionally chosen to minimise misleading comparative interpretations in the presence of baseline imbalances; therefore, causal conclusions regarding comparative effectiveness between treatments cannot be drawn. Despite these limitations, the large real-world population, longitudinal design and consistent findings across clinician-reported and patient-reported outcomes support the robustness of the observed response trajectories and provide meaningful insights into treatment dynamics in patients with moderate-to-severe AD treated in routine clinical practice.

CONCLUSIONS

In this large multicentre real-world cohort, both dupilumab and upadacitinib demonstrated rapid, sustained and progressively accumulating clinical benefits in adults with moderate-to-severe AD. Upadacitinib showed faster early response kinetics, whereas dupilumab exhibited a steady and continuous increase in response rates over time, leading to convergence of categorical response rates at long-term follow-up. High rates of deep clinical response, including complete skin clearance, were achieved with both therapies at 52 weeks. These findings highlight the importance of evaluating longitudinal treatment trajectories rather than isolated timepoints and may support a personalised, mechanism-informed therapeutic approach in routine clinical practice, although the descriptive nature of the analysis should be considered when interpreting comparative outcomes.

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Ethical Approval. This work is a retrospective analysis conducted exclusively on fully anonymized clinical data, with no possibility of identifying individual patients and without any intervention or modification of clinical practice. According to Italian national regulations, including the provisions of the Italian Data Protection Authority (Garante per la Protezione dei Dati Personali), in particular General Authorisation No. 9/2016 and its subsequent alignment with the EU General Data Protection Regulation (EU Regulation 2016/679, GDPR), anonymized data are not considered personal data, and their use for research purposes does not require ethical committee approval. This regulatory interpretation is consistent with major international ethical frameworks, including the Declaration of Helsinki (2013, Article 32) and ICH-GCP E6(R2), which specify that ethical review is not required when research is conducted on pre-existing, fully anonymized data.

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