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REVIEW

Drug Survival, Retention, and Persistence of Dupilumab in Adults and Adolescents with Atopic Dermatitis: A Narrative Literature Review

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ABSTRACT

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin condition that can have a negative impact on a patient's quality of life. Long-term effectiveness is required to manage the symptoms of AD (skin inflammation, eczematous lesions, and itching). Because some of the systemic immunosuppressants used to treat AD have been associated with serious adverse events (AEs), other safer, more effective options, including dupilumab, have been proven effective long-term for treatment of adult and adolescent patients with moderate-to-severe AD. The long-term safety and effectiveness of a drug are usually confirmed in real-world studies by evaluating its performance over time. Measures such as drug survival, drug retention, drug persistence, or retention rates reflect whether treatment may be considered as satisfactory by both patients and physicians, meeting key clinical needs. This review aimed to describe the survival, retention, or persistence of dupilumab therapy in adults and adolescents with moderate-to-severe AD by conducting a PubMed search in March 2023 and screening for relevant publications. Globally, real-world studies with dupilumab have regularly reported high drug survival rates after 1, 2, and 3 years of observation, being consistently at 80–90%, with low rates of treatment discontinuation due to lack of efficacy or AEs. These findings are notably higher than 1- and 2-year drug survival rates of systemic immunosuppressants (including cyclosporine [37% and 20%, respectively] and methotrexate [41% and 33%, respectively]). Overall, real-world data on drug survival have confirmed that dupilumab

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provides long-term sustained efficacy and acceptable safety in patients with moderate-to-severe AD.

Keywords: Atopic dermatitis; Drug survival; Dupilumab; Persistence; Retention

Key Summary Points

Atopic dermatitis is a chronic, relapsing inflammatory systemic condition that strongly impacts patient quality of life.
Effective long-term management is required with various therapeutic agents, including systemic immunosuppressants, which are associated with serious adverse events that can lead to poor compliance to treatment or treatment discontinuation.
Drug survival, retention, and persistence are comprehensive outcome measures that reflect both the effectiveness and tolerability of a drug, and are reliable indicators of drug performance in routine practice.
Real-world studies of dupilumab have shown prolonged drug survival, sustained drug retention, and prolonged drug persistence compared with systemic immunosuppressants, confirming its long-term effectiveness and acceptable safety profile in adult and adolescent patients with moderate-to-severe atopic dermatitis.

INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing systemic disease characterized by skin inflammation, eczematous skin lesions, and itching [1, 2], affecting up to 20% of children [3] and 4.9% of adults globally [4]. The prevalence of AD in adulthood tends to be higher in South European countries, such as Italy (8.1%) [4]. The characteristic itch associated with AD is considered the most burdensome symptom, with a profound impact on patient daily life, as well as a cause of significant sleep disruption [5, 6]. While the etiology of AD remains to be fully elucidated, there is evidence implicating both genetic and environmental factors in its development [7]. The pathophysiology of AD is complex and multifactorial, resulting from skin barrier dysfunction and innate or adaptive immune dysregulation [7]. Type 2 inflammation plays a pivotal role in the pathogenesis of AD, particularly by means of key effector cytokines, such as interleukin (IL)-4 and IL-13 [8].

As a chronic disease, moderate-to-severe AD requires long-term management, including avoidance of trigger factors (i.e., allergens, and/or mechanical, chemical, or biological irritants), proper skin care (i.e., cleansing and moisturizing), topical anti-inflammatory therapy (e.g., corticosteroids and calcineurin inhibitors), phototherapy, and systemic drugs [1, 2]. Despite the availability of both topical (i.e., emollients, moisturizers, corticosteroids) and systemic (i.e., oral corticosteroids, immunosuppressants) treatment options, control of moderate-to-severe AD remains suboptimal in many patients, thereby negatively impacting their quality of life (QoL) [9–12]. Although the use of ultraviolet B (UVB) phototherapy to treat AD has increased steadily since the 1980s, it is time consuming and not easily available for all patients; additionally, the safety of exposing the skin to UVB light needs to be further evaluated [13].

Many of the available systemic immunosuppressant treatments for AD are associated with adverse events (AEs) that frequently render them unsuitable for continuous, long-term use [1, 2]. More specifically, systemic corticosteroids are frequently used to treat severe AD exacerbations; however, this treatment is not recommended for longer than 2 weeks, and patients' symptoms often rebound after treatment discontinuation [1, 14]. Cyclosporine treatment requires monitoring for AEs, including nephrotoxicity and hypertension, and has a maximum recommended treatment duration of 1 year in the USA and 2 years in Europe as a result of safety concerns [1, 14]. Other systemic immunosuppressants, including methotrexate, mycophenolate mofetil, and azathioprine, which are frequently used off-label in the treatment of patients with

moderate-to-severe AD, have been reported to be associated with serious AEs [1, 15].

Recently, biologic drugs such as dupilumab, tralokinumab, and small molecules targeting type 1 Janus kinase (JAK1) inhibition have been approved for the treatment of AD in several countries following the successful completion of phase 3 trials [16–18]. Dupilumab is a fully human immunoglobulin (Ig) G4 monoclonal antibody that binds to the α-subunit of the IL-4 receptor (IL-4Rα) shared by the IL-4 and IL-13 receptor complexes, inhibiting the signaling of these key type 2 inflammatory cytokines [19, 20]. Dupilumab was first approved by the US Food and Drug Administration and by the European Medicines Agency in 2017 for use in adults with moderate-to-severe AD, and then within a few years also in adolescents and children from 6 months of age [16]. Of note, in some European countries, dupilumab is only approved for adult patients with severe AD who are unresponsive to or do not tolerate other systemic treatment options, mainly cyclosporine, as is the case in Italy [21].

The safety and efficacy of dupilumab in the treatment of adults, adolescents, and children from 6 months of age with moderate-to-severe AD have been demonstrated in several randomized controlled trials (RCTs) [22–32]. In these RCTs, dupilumab with or without topical corticosteroids consistently improved the clinical signs and symptoms of AD compared with placebo, with improvements also seen in measures of sleep and QoL.

Since RCTs typically enroll a selected patient population and test the therapeutic efficacy of a drug under an ideal set of circumstances, the results of these trials do not always translate to real-world clinical practice [33]. RCTs of dupilumab have evaluated the efficacy and safety of treatment for up to 16 weeks [22, 23, 25–29], although two of the trials evaluated dupilumab for up to 52 weeks [24, 30]. Long-term data from open-label extension studies of dupilumab have shown clinically relevant improvements in both physician- and patient-reported outcome measures after up to 5 years of treatment, with an acceptable safety profile [17, 34–37]. Furthermore, real-world data suggest that dupilumab addresses the unmet need for a well-tolerated long-term therapeutic agent for patients with AD [38].

Patient perception of AD treatment is an important part of the risk/benefit analysis, with patient assessment now forming an essential component of treatment response [39]. Evaluation of the real-world use of dupilumab will indicate whether the ongoing needs of patients with AD are met. For the purposes of this review, we have considered the closely related concepts of drug survival, drug retention, and drug persistence as duration of time from initiation of drug therapy until discontinuation, and survival, persistence, or retention rate as the proportion of patients continuing a medication at a specific point in time, of dupilumab [40–43]. These measures reflect the continual acceptability of a medicine by patients [40, 44, 45] by estimating the cumulative probability of the patient remaining under treatment until discontinuation, and take into account drug effectiveness, safety, and patient and clinician preferences [44]. All these terms differ from treatment compliance or adherence, which are measures of how well a patient conforms to the instructions for taking their medication, with respect to timing, dosage, and frequency [40]. Drug survival, retention, and persistence are comprehensive outcome measures that reflect both the effectiveness and tolerability of the drug [45], and they are reliable reflections of drug performance in routine practice [44, 46–48]. Behavioral factors, such as treatment adherence, can indirectly influence drug retention; for example, doctors may be unaware that nonadherence is the reason for patient-perceived decrease in treatment effectiveness, and may switch patients to a different drug [48].

The aim of this literature review is to describe the data available worldwide on dupilumab treatment performance by reviewing studies on drug survival, retention, or persistence, in order to provide a measure of the efficacy and safety of dupilumab when used to treat patients in daily practice, and to gauge the acceptance of the drug by adults and adolescents with moderate-to-severe AD.

DATA SOURCES AND SEARCH STRATEGY

A PubMed search was conducted on March 2, 2023, using the search string (dupilumab AND (compliance OR persistence OR adherence OR retention OR drug survival)). Results were manually screened for publications relevant to drug survival, retention, and/or persistence rates in adults or adolescents receiving dupilumab for the treatment of AD. Reports with no data on dupilumab retention, case reports, studies in children (aged 6 months to 11 years), and those describing indications other than AD were excluded. Additional studies were identified by checking the reference lists from the studies retrieved from the above search and from the authors' knowledge of the subject. In total, 65 publications, guidelines, and/or online resources were used in this review.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

PERFORMANCE OF DUPILUMAB IN ADULTS WITH ATOPIC DERMATITIS

Several observational studies have provided useful data on dupilumab drug retention across a range of timeframes in real-world clinical practice (Table 1). A real-world, 48-week retrospective multicenter study of dupilumab in Italian patients with moderate-to-severe AD showed high dupilumab drug survival rates (106/109; 97%) at weeks 4 and 16 that remained high through to week 48 (98/109; 90%; Table 1) [49]. Similarly, two other Italian retrospective studies in patients with AD have shown high drug survival rates with long-term dupilumab therapy, with 82% remaining on treatment at 16 months (64 weeks) [44], and 87% at 72 weeks [50], respectively. These results were consistent with a prospective study conducted in Northeastern Italy, where dupilumab drug survival was evaluated among 363 patients with moderate-to-severe AD [51]. After almost 5 years, 319 patients (88%) were still using dupilumab and 44 (12%) had discontinued treatment because of ineffectiveness ($n=11$), AEs ($n=20$), pregnancy ($n=5$), AD remission ($n=8$), or loss to follow-up ($n=5$). The overall dupilumab drug survival rate at 4 years was 76% [51].

Other European real-world studies have also reported high rates of dupilumab drug survival, retention, or persistence (Table 1). In the retrospective analysis from the BIOREP registry study including 360 Czech patients treated with dupilumab for severe AD, drug survival rates remained high (>90%) for up to 24 months [52]. The most common reasons for discontinuation in this study were lack of effectiveness, noncompliance, and AEs (each occurring in approximately 1% of patients). Likewise, prospective data on dupilumab from the BioDay registry in the Netherlands reported overall drug survival rates of 90% at 1 year, 86% at 2 years, and 79% at 3 years (Fig. 1a) [47]. In a retrospective Portuguese study of long-term dupilumab persistence in 169 patients with AD (27 adolescents and 142 adults), only nine patients (5%) discontinued therapy after 48 weeks, four because of lack of efficacy, four because of AEs, and one for a reason that was not reported [53]. Similar results were also observed in a retrospective Spanish study in 240 adults with moderate-to-severe AD, in whom dupilumab drug survival rates were 94% after 20 months (Fig. 1b) [46]. Dupilumab drug survival, retention, or persistence data are also available from real-world studies conducted in North America (Table 1). In a retrospective Canadian real-world study including 145 patients with AD, drug survival with dupilumab treatment was 80% after 104 weeks [54].

Although the coronavirus disease-2019 (COVID-19) pandemic seemed to give rise to a worldwide increase in concern regarding the use of biologic agents in patients at dermatology clinics, a study from early 2020 in the USA reported that only 1 of 162 patients temporarily discontinued treatment because of patient-driven COVID-19 concerns [55]. Data from Italy suggested that while fear of COVID-19 exposure was one of the main causes of dupilumab treatment interruption, treatment discontinuation

Table 1 Summary of data on dupilumab retention rates

Country	Reference	Dupilumab drug survival rate (time of observation)	Type of study (*n*)
Canada	Georgakopoulos et al. 2021 [54]	97% (week 16) 83% (week 52) 80% (week 104)	Retrospective, multicenter (*n* = 145)
Czech Republic	Kojanova et al. 2022 [52]	98% (4 months) 97% (6 months) 96% (12 months) 93% (18 months) 93% (24 months)	Retrospective, multicenter (*n* = 360)
Germany	Stölz et al. 2022 [63]	95% (12 months) 89% (24 months)	Prospective (*n* = 1211)
Italy	Dal Bello et al. 2020 [44]	82% (16 months)	Retrospective, single-center (*n* = 149)
	Fargnoli et al. 2022 [49]	93.5% (week 24) 90% (week 48)	Retrospective, multicenter (*n* = 109)
	Napolitano et al. 2022 [50]	87% (week 72)	Retrospective, multicenter (*n* = 247)
	Pezzolo et al. 2023 [51]	91% (1 year) 83% (2 years) 79% (3 years) 76% (4 years)	Prospective (*n* = 363)
Netherlands	Spekhorst et al. 2022 [47]	90% (1 year) 86% (2 years) 79% (3 years)	Prospective data from National Registry (*n* = 402)
Portugal	Torres et al. 2022 [53]	95% (week 48)	Retrospective, multicenter (*n* = 169)
Spain	Pereyra-Rodriguez et al. 2021 [46]	94% (20 months)	Retrospective, multicenter (*n* = 240)
USA	Khosravi et al. 2020 [59]	89% (800 days)	Retrospective, single-center (*n* = 112)

during the COVID-19 pandemic was low [56]. This was corroborated by a multicenter Italian report, which found that even a 16-week COVID-19-related interruption in dupilumab therapy did not cause any significant relapses or worsening of AD [57].

Dupilumab has demonstrated a good safety profile after more than 5 years in clinical practice [58]. In a US retrospective study, of 112 treated patients, 9 discontinued dupilumab because of AD flare (5%), conjunctivitis (3%), and adequate control with phototherapy (0.9%), with 89% of patients remaining on dupilumab at 800 days of treatment [59]. An analysis of randomized, placebo-controlled AD clinical trials of dupilumab in AD confirmed that placebo-treated patients had a lower incidence of conjunctivitis (2.1–11.1%) than dupilumab-treated patients (8.6–22.1%); interestingly, the incidence of conjunctivitis was

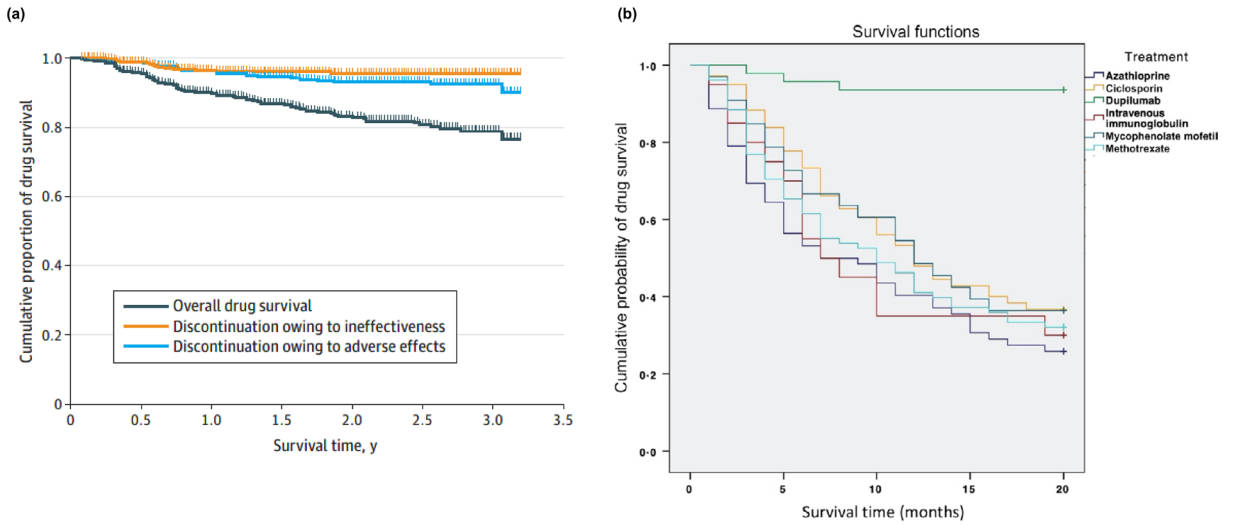

Fig. 1 **a** Dupilumab drug survival in the overall population and in patients who discontinued because of ineffectiveness or adverse effects over 3.5 years in the BioDay registry study in 715 patients with moderate-to-severe atopic dermatitis (AD) [47]. Reproduced with permission from [JAMA Dermatology, Dupilumab drug survival and associated predictors in patients with moderate to severe atopic dermatitis long-term results from the Daily Practice BioDay registry. 2022. 158(9):1048–1056]. Copyright©(2022) American Medical Association. All rights reserved. **b** Comparative drug survival rates for systemic and biologic treatments according to Kaplan–Meier analysis at 20 months in 240 patients with AD in a Spanish retrospective study [46]. Reproduced from Pereyra-Rodriguez JJ, Domínguez-Cruz J, Ruiz-Villaverde R, Silvestre JF, Galán M, Curto L, Figueras I, Serra-Baldrich E, Armario-Hita JC. Drug survival of systemic and biological treatments for moderate-to-severe atopic dermatitis in adults: a multicenter retrospective observational study, Br J Dermatol, 2021, 184, 1, 175–176, by permission of Oxford University Press

linked to both the severity of AD and the patient's prior history of conjunctivitis [60].

DUPILUMAB PERFORMANCE IN COMPARISON WITH OTHER SYSTEMIC AGENTS

Several studies have compared dupilumab drug survival, retention, or persistence with that of other systemic agents, largely used off-label, for the treatment of patients with AD. In a comparison of dupilumab drug survival data from the BioDay registry ($n=402$) with those from historical cohorts of patients receiving cyclosporine ($n=356$) or methotrexate ($n=89$), the overall drug survival rate at 1 year and 2 years was significantly greater for dupilumab (91% and 88%, respectively) versus cyclosporine (37% and 20%, respectively) or methotrexate (41% and 33%, respectively; $P<0.0001$ for all comparisons) [61]. Approximately half of the patients discontinued cyclosporine and methotrexate because of treatment failure (defined as lack of treatment effect or adverse effects) [61]. The Spanish multicenter, retrospective, observational study also found significantly higher drug survival rates for dupilumab (94%; $n=47$) than for cyclosporine (37%; $n=180$), methotrexate (32%; $n=78$), azathioprine (27%; $n=62$), mycophenolate mofetil (36%; $n=33$), or intravenous Ig (30%; $n=20$) after 20 months ($P<0.001$ for dupilumab vs all other therapies; Fig. 1b) [46]. The most common reasons for discontinuation of systemic therapies included AEs and primary treatment failure [46].

A separate German study compared cumulative drug survival rates and reasons for drug discontinuation of cyclosporine (as the reference treatment), dupilumab, azathioprine, methotrexate, and mycophenolate mofetil prescribed

under real-world conditions ($n=94$) in adults with AD treated at two dermatology departments [62]. In this study, dupilumab was the only treatment associated with a significantly higher probability of drug survival and a lower probability of treatment discontinuation over time than cyclosporine. Compared with cyclosporine, the risk of treatment discontinuation was 90% lower with dupilumab (hazard ratio [HR] 0.10; 95% confidence interval [CI] 0.01–0.73; $P=0.024$), 13% lower for methotrexate (HR 0.87; 95% CI 0.35–2.12), 2% lower for mycophenolate mofetil (HR 0.98; 95% CI 0.60–1.59), and 18% higher for azathioprine (HR 1.18; 95% CI 0.55–2.49) [62]. In addition, AEs were the most common reason for treatment interruption with cyclosporine, azathioprine, and methotrexate; only one patient (6%) discontinued dupilumab before the end of the observation period, due to treatment ineffectiveness [62].

Other studies comparing dupilumab with cyclosporine have shown similar results. When evaluating cyclosporine drug survival rates, it is important to note that most guidelines do not recommend continuous cyclosporine therapy for more than 1–2 years [63]. In an interim analysis of data from the TREAT Germany registry, a large, prospective AD registry of more than 1400 patients with moderate-to-severe AD, data from patients treated with dupilumab ($n=369$) or cyclosporine ($n=41$) were analyzed [63]. At 12 and 24 months, discontinuation rates were 5% and 11%, respectively, for dupilumab versus 78% and 100%, respectively, for cyclosporine. The most common reasons for cyclosporine discontinuation were AEs (31%) and insufficient efficacy (27%); 19% of those who discontinued cyclosporine subsequently received dupilumab [63]. In a further comparative study of dupilumab versus cyclosporine in patients with severe AD ($n=251$), the overall probability of patients remaining on treatment at 16 months was 82% with dupilumab and 11% with cyclosporine ($P<0.001$); the most frequent reason for dupilumab discontinuation was persistent clinical remission (7%), and the most frequent reasons for cyclosporine discontinuation were extracutaneous AEs (24%), persistent clinical remission (16%), and minimal or no improvement (12%) [44].

In a retrospective study of adults with severe AD, comparing dupilumab ($n=247$) and cyclosporine ($n=95$) drug survival, only 13% of patients in the dupilumab group had discontinued treatment by week 72 (mean treatment duration 35 weeks), yielding a dupilumab drug survival rate of 87% compared with 21% for cyclosporine [50]. It is significant that the most common reason for dupilumab discontinuation was the achievement of complete disease remission (13/32; 41%) after a mean of 42 weeks' treatment. In cyclosporine-treated patients, 71% had discontinued treatment by week 72, while 8/95 (8%) were lost to follow-up during the first 12 weeks. The predominant cause of treatment withdrawal in the cyclosporine group was AEs (28/67; 42%) [50].

Overall, dupilumab should be considered an effective and well-tolerated treatment to enhance clinical response to AD owing to its favorable safety profile, low withdrawal rates, and enhanced clinical response when compared with other systemic treatments (cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil) [62]. Other available treatments for adults with moderate-to-severe AD include the IL-13 inhibitor tralokinumab and JAK1 inhibitors (e.g., abrocitinib, baricitinib, and upadacitinib) [64]. However, real-world data comparing drug survival, retention, or persistence rates of dupilumab with anti-IL-13 monoclonal antibodies and other new targeted therapies are not yet available.

DRUG PERFORMANCE OF DUPILUMAB IN ADOLESCENTS WITH ATOPIC DERMATITIS

In the Portuguese study described above, none of the 27 adolescents included in the study had discontinued dupilumab after 48 weeks of treatment [53]. An Italian multicenter study of 139 adolescents with moderate-to-severe AD treated with dupilumab reported that 131 adolescents completed 32 weeks of therapy (94.2%); four contracted COVID-19 and temporarily stopped dupilumab and four discontinued treatment permanently (one because of a car accident and

three were lost to follow-up) [65]. At the end of week 52, the dupilumab drug survival rate was 87.1% ($n=121$), with three adolescents temporarily stopping treatment as a result of COVID-19 infection. A further seven patients were lost to follow-up and three discontinued because of inefficacy and AEs (conjunctivitis in one and flushing in both) [65]. A study by Napolitano et al. (2022) [50] on adolescents undergoing dupilumab therapy for AD ($n=27$) revealed that the AEs that were experienced were mild and did not lead to treatment discontinuation in any patients after 24 weeks (100% survival rate).

STRENGTHS AND LIMITATIONS

This narrative literature review of data from numerous real-world studies provides a detailed evaluation of drug survival, retention, and persistence rates for dupilumab long-term. In addition to its established efficacy and safety in real-world clinical practice, dupilumab exhibits survival rates of 80–90% after up to 5 years of treatment. However, it is important to note that dupilumab drug retention rates may be inflated in such studies as a result of the lack of available alternative treatment options [61]. Future studies should include control groups for multiple comparisons and more detailed evaluations of individual patient responses. Additional studies could be conducted to examine the experiences of different subgroups of patients (e.g., defined by disease severity at baseline, failure of prior therapy, or duration of observation).

CONCLUSIONS

Overall, data from real-world observational studies consistently report high rates of dupilumab drug survival, retention, and persistence, providing strong evidence that patients and clinicians perceive dupilumab to be a satisfactory and acceptable treatment. Additionally, in real-world clinical practice dupilumab exhibits high effectiveness and is well tolerated with continued therapy, even with the development of other unexpected diseases, such as COVID-19 infection. Dupilumab drug survival rates for 1, 2, and 3 years or longer consistently range from 80% to 90%, with low rates of treatment discontinuation due to lack of efficacy or AEs. This is in contrast with systemic immunosuppressants, such as cyclosporine and methotrexate, which typically have higher rates of discontinuation than dupilumab. Taken together, these results suggest that dupilumab is associated with higher rates of drug survival compared with other traditional systemic agents for the treatment of patients with moderate-to-severe AD. Data on dupilumab drug survival, retention, and persistence represent an important proxy of its elevated and sustained efficacy and acceptable long-term safety in treating adults and adolescents with moderate-to-severe AD.

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Declarations

Conflict of Interest. Mariateresa Rossi is a consultant, advisory board member, and

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