ORIGINAL REPORT

Long-term Outcomes of New Systemic Agents in Atopic Dermatitis: Drug Survival Analyses and Treatment Patterns in Daily Practice

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In recent years, several new systemic agents (biologics and Janus kinase inhibitors [JAKi]) have been registered for the treatment of moderate-to-severe atopic dermatitis (AD). However, comparisons of real-world drug survival data and insights into treatment patterns of these advanced systemics are limited. Data from a prospective observational single-centre registry were collected from 549 adult AD patients (759 treatment courses) receiving biologics (dupilumab, tralokinumab) or JAKi (abrocitinib, baricitinib, upadacitinib) and analysed using Kaplan–Meier survival curves. Cox regression analyses were used to evaluate predictors of survival. Frequencies and percentages summarized data on the initial and subsequent treatments received, with a Sankey diagram illustrating the switching patterns. The 18-month overall drug survival rates for dupilumab, abrocitinib, upadacitinib, tralokinumab, and baricitinib were 70.0%, 51.5%, 48.4%, 39.4%, and 20.4%, respectively. No significant predictors for drug survival were identified. Dupilumab was the predominant initial treatment (87.2%) and upadacitinib the most frequently used second and third treatment. In the total cohort, 57.9% of patients remained on their initial treatment and 26.8% switched to other treatments. In conclusion, dupilumab showed superior survival rates while baricitinib had the lowest survival rate. Frequent switching highlights the need for biomarkers that predict response to advanced systemic treatments to improve attrition rates.

Key words: analysis; survival; atopic dermatitis; biologics; Janus kinases.

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SIGNIFICANCE

This study looked at how effective different new treatments for eczema were over time, which treatments were chosen, and how often people switched from one treatment to another. Dupilumab was the most prescribed initial treatment and showed the best treatment results, with 70% of patients still using dupilumab after 18 months, while baricitinib was used by only >20% patients at 18 months. It is important to note that dupilumab was the first and only advanced treatment available for several years. Almost 27% of patients switched to second treatments, highlighting the need for more personalized treatment strategies.

Approximately 15% of patients diagnosed with atopic dermatitis (AD) are classified as having moderate-to-severe disease. These patients often require conventional systemic immunosuppressants to achieve disease control. In the Dutch healthcare system, patients can be treated with new systemic agents if conventional systemics fail (1). Currently 2 biologics and 3 Janus kinase inhibitors (JAKi) are approved and reimbursed for treatment of moderate to severe AD in the Netherlands. Dupilumab selectively inhibits the IL-4 receptor alpha chain, whereas tralokinumab specifically binds to IL-13. JAKi target the JAK-STAT pathway, a key regulator of various inflammatory pathways. Baricitinib inhibits both the JAK1 and JAK2 pathways, whereas upadacitinib and abrocitinib specifically target the JAK1 pathway. Several clinical trials have demonstrated the efficacy and safety of these biologics and JAKi for the treatment of AD (2–6).

Despite expanding therapeutic options, it is crucial to evaluate the effectiveness and safety of biologics and JAKi in daily practice. While real-world drug survival studies, including those for dupilumab, have been published (7, 8), limited data are available for the other new systemic agents and comparisons of their long-term drug survival. Drug survival analyses provide valuable insights into the timing and reasons for treatment discontinuation, such as inadequate disease control or adverse events (AEs). In addition, drug survival analyses enable comparisons between different treatments without comparative RCTs, shedding light on potential differences in treatment durability beyond the conventional duration of clinical studies. This information may help clinicians and patients in making well-informed decisions, understanding the associated benefits and risks of each treatment.

Although several advanced systemics are available, there remains an unmet need for patients with AD shown by the variability in treatment response, and a subset of patients not achieving adequate disease control (9–13). Treatment patterns can provide information on first and subsequent treatments received, switching patterns, non-switching, and discontinuation. This study presents real-world data on drug survival of dupilumab, tralokinumab,

abrocitinib, baricitinib, and upadacitinib in AD patients. Additionally, we investigated predictors of drug survival and evaluated treatment patterns in AD patients initiating biologic or JAKi treatment in daily practice.

MATERIALS AND METHODS

Design

Data were collected from the Erasmus MC IMID Quality of Care Registry, a prospective, single-centre, observational cohort study of AD patients. The study was conducted at the Department of Dermatology, Erasmus University Medical Center, Rotterdam, the Netherlands. All AD patients ≥18 years who started a new systemic treatment, biologics (dupilumab, tralokinumab) or JAKi (abrocitinib, baricitinib, upadacitinib), in the context of standard care between January 2017 and February 2023 were included (14) . This study was approved by the institutional review board of Erasmus MC (MED-2017-1123).

Patient and treatment characteristics

The following patient characteristics were extracted from the electronic health records: sex, age at start of treatment, age of onset of disease, atopic comorbidities, Fitzpatrick skin types, BMI, and previously used conventional immunosuppressants. Patients treated with dupilumab or tralokinumab received a loading dose of 600 mg and started on a treatment regimen of 300 mg every 2 weeks. Patients receiving abrocitinib, baricitinib, or upadacitinib were treated with 50–100–200 mg, 2–4 mg, or 15–30 mg daily, respectively (15). Treatment type, discontinuation, duration of treatment at discontinuation, reason for discontinuation, dose reduction, and systemic concomitant treatment were recorded. After starting treatment with biologics and JAKi, concomitant conventional immunosuppressants were either discontinued within 3 months or tapered and continued at a low dose. Follow-up started at the initiation of treatment and ended when the drug was either discontinued or switched to a new treatment. Interruption of treatment with a biological or JAKi for less than 90 days or less than 14 days, respectively, was coded as treatment continuation. Only the initial course of each treatment was included in the analysis, ensuring that each patient was represented only once within each treatment group. Treatment courses were analysed independently, permitting patients to be included in multiple treatment groups if they transitioned between treatments during the study period.

Statistical analysis

Patient characteristics were reported as median and interquartile range (IQR) for continuous variables, and categorical data were reported as the number of patients and percentage (*n*, %). Missing data were reported and excluded from the analyses. Kaplan–Meier survival curves were used to analyse the overall survival for each treatment and survival at 6 and 18 months was reported. Additional drug survival curves were analysed separately for discontinuation due to AEs and ineffectiveness. Discontinuation of treatment due to both AEs and ineffectiveness was reported as an event in the analyses of overall drug survival, ineffectiveness, and adverse events. Patients were censored if they were still receiving treatment at the time of data lock or if they were lost to follow up. Because in daily practice doses are frequently increased or decreased, analyses for different dosages were not performed. Cox proportional hazards regression analyses were conducted to evaluate the impact of predictors on the overall drug survival (Appendix S1). We evaluated frequencies and percentages on the initial and subsequent treatments received. Initial treatment refers to the first administration of a new systemic agent (biological or JAKi). Sankey diagrams were used to show patterns of switching between treatments and were generated using the R statistical software (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria). Statistical analyses were performed with the R statistical software and IBM SPSS Statistics for Windows, version 28.0.1.0 (IBM Corp, Armonk, NY, USA). Figures were created using GraphPad Prism (version 9; https://www.graphpad.com/) (Appendix S1).

RESULTS

Baseline characteristics

A total of 549 AD patients (759 treatment courses) with a median age of 37 years (IQR 29–54) were analysed. 46.8% were female and the age of onset of disease was 0–12 years in most patients (72.3%). Most patients (97.6%) had previously received traditional systemic immunosuppressants, with 39.3% having received 3 or more systemic immunosuppressants, indicating a cohort with (moderate-to-) severe AD patients. Baseline characteristics of each treatment course are presented in **Table I**, including 492 (64.8%) dupilumab, 51 (6.7%) tralokinumab, 43 (5.7%) abrocitinib, 62 (8.2%) baricitinib, and 111 (14.6%) upadacitinib courses. Notable differences between the treatment groups included a higher median age in the baricitinib group (42 years, [29–60]). See Fig. S1 for treatment prescriptions over time and dates of treatment add-on.

Treatment characteristics

Table II lists the treatment characteristics of each treatment. Overall median treatment follow-up was 10 months (IQR 4–28) and median treatment duration at discontinuation was 6 months (IQR 3–14). In total, 24.2% of treatment courses were discontinued due to ineffectiveness. Biologic and JAKi dose reductions were successful in 19.6% of treatment courses, including 26.2% of dupilumab courses. In 42.7% of treatment courses, patients used concomitant immunosuppressive treatments when starting biologics, but in most cases concomitant immunosuppressants were discontinued in the first 3 months.

Drug survival

Dupilumab ($n=492$) shows the most favourable drug survival with a median overall drug survival of 19 months (IQR 7–38) and an overall drug survival at 6 and 18 months of 86.8% and 70.0% respectively (**Fig. 1**A). In patients who discontinued dupilumab due to ineffectiveness, the overall survival rates were 92.3% and 83.1% at 6 and 18 months respectively (Fig. 1B). For patients who discontinued dupilumab due to AEs ($n=83$), drug survival rates were 93.3% and 86.3% at 6 and 18 months, respectively (Fig. 1C). In contrast, tralokinumab ($n=51$)

Table I. Characteristics of treatment courses (*n* = 759) in 549 AD patients treated with dupilumab, tralokinumab, abrocitinib, baricitinib, or upadacitinib

	Biologics		JAK inhibitors		
	Dupilumab (*n*=492)	Tralokinumab (*n*=51)	Abrocitinib (*n*=43)	Baricitinib (*n*=62)	Upadacitinib (*n*=111)
Female sex, *n* (%)	235 (47.8)	20 (39.2)	19 (44.2)	29 (46.8)	47 (42.3)
Age at start of advanced systemic treatment, years, median (IQR)	34 (26–51)	32 (26–49)	30 (25–41)	42 (29–60)	36 (26–51)
BMI, median (IQR)	24.9 (22.3–27.9)	25.0 (21.8–27.5)	24.9 (21.5–26.8)	25.8 (23.0–29.2)	24.8 (23.1–27.7)
- Missing, *n* (%)	189 (38.4)	17 (33.3)	18 (41.9)	25 (40.3)	53 (47.7)
Treatment courses, *n* (%)					
- Total	492 (100.0)	51 (100)	43 (100.0)	62 (100.0)	111 (100.0)
- Naive for immunosuppressive drugs, *n* (%)	8 (1.6)	2 (3.9)	2 (4.7)	4 (6.5)	3 (2.7)
- 1 prior immunosuppressive drug, *n* (%)	94 (19.1)	13 (25.5)	8 (18.6)	9 (14.5)	20 (18.0)
- 2 prior immunosuppressive drugs, *n* (%)	192 (39.0)	15 (29.4)	12 (27.9)	19 (30.6)	43 (38.7)
- ≥ 3 prior immunosuppressive drugs, *n* (%)	198 (40.2)	21 (41.2)	21 (48.8)	30 (48.4)	45 (40.5)
Age of onset of disease, years					
- Childhood (0–12 years) *n* (%)	365 (74.2)	40 (78.4)	34 (79.1)	40 (64.5)	77 (69.4)
- Adolescence (12–18 years) *n* (%)	20 (4.1)	2 (3.9)	1 (2.3)	1 (1.6)	4 (3.6)
- Adulthood (>18 years) *n* (%)	75 (15.2)	5 (9.8)	7 (16.3)	14 (22.6)	21 (18.9)
- Missing	32 (6.5)	4 (7.8)	1 (2.3)	7 (11.3)	9 (8.1)
Atopic comorbidity					
- Allergic asthma, *n* (%)	287 (58.3)	30 (58.8)	22 (51.2)	26 (41.9)	63 (56.8)
- Allergic conjunctivitis, *n* (%)	140 (28.5)	20 (39.2)	16 (37.2)	16 (25.8)	34 (30.6)
- Allergic rhinitis, *n* (%)	349 (70.9)	40 (78.4)	30 (69.8)	38 (61.3)	75 (67.6)
- None, *n* (%)	74 (15.0)	5 (9.8)	6 (14.0)	17 (27.4)	19 (17.1)
- Missing, *n* (%)	6 (1.2)	1 (2.0)	0	0	0
- Family history of AD, *n* (%)	219 (44.5)	21 (41.2)	21 (48.8)	23 (37.1)	46 (41.4)
- Missing, *n* (%)	58 (11.8)	8 (15.7)	5 (11.6)	10 (16.1)	17 (15.3)
Fitzpatrick skin types, *n* (%)					
- I	27 (5.5)	1 (2.0)	1 (2.3)	4 (6.5)	3 (2.7)
- II	312 (63.4)	38 (74.5)	35 (81.4)	40 (64.5)	72 (64.9)
- III	49 (10.0)	8 (15.7)	1 (2.3)	10 (16.1)	12 (10.8)
- IV	53 (10.8)	3 (5.9)	2 (4.7)	1 (1.6)	14 (12.6)
- V	40 (8.1)	1 (2.0)	3 (7.0)	4 (6.5)	7 (6.3)
- VI	9 (1.8)	0	1 (2.3)	3 (4.8)	3 (2.7)
- Missing	2 (0.4)	0	0	0	0
Immunosuppressive drugs history, *n* (%)					
- Cyclosporine A, *n* (%)	432 (87.8)	46 (90.2)	40 (93.0)	53 (85.5)	101 (91.0)
- Methotrexate, *n* (%)	170 (34.6)	17 (33.3)	21 (48.8)	31 (50.0)	45 (40.5)
- Azathioprine, *n* (%)	58 (11.8)	6 (11.8)	8 (18.6)	13 (21.0)	14 (12.6)
- Mycophenolic acid, *n* (%)	137 (27.8)	11 (21.6)	11 (25.6)	20 (32.3)	29 (26.1)
- Systemic steroids <2 weeks, *n* (%)	330 (67.1)	33 (64.7)	30 (69.8)	(69.4)	73 (65.8)
- Systemic steroids >3 weeks, *n* (%)	14 (2.8)	0	0	2 (3.2)	3 (2.7)
- Missing, *n* (%)	0	0	0	0	1 (0.9)
Year start advanced systemic					
- 2017–2020, *n* (%)	301 (61.2)	3 (5.9)	0	10 (16.1)	0
- 2021–2023, *n* (%)	191 (38.8)	48 (94.1)	43 (100.0)	52 (83.9)	111 (100.0)

Patients may have received multiple different treatments over time, resulting in representation across several treatments in the Table (e.g., dupilumab, tralokinumab). Only the initial course of each treatment was included in the analysis, ensuring that each patient was represented only once within each treatment group.
n: number of treatment courses; AD: atopic dermatitis; IQR: interquartile range.

showed a median overall drug survival of 5 months (IQR 2–7) with lower survival rates at 6 and 18 months of 62.9% and 39.4%, respectively (Fig. 1A). For discontinuation due to ineffectiveness (*n*=17), drug survival rates of tralokinumab were 74.1% and 46.5% at 6 and 18 months, respectively (Fig. 1B). The drug survival rates for AEs were higher at 85.7% at both 6 and 18 months (*n*=6) compared with the drug survival rates split for ineffectiveness (Fig. 1C).

In addition to dupilumab, upadacitinib and abrocitinib also showed good drug survival rates. The median overall drug survival rate for upadacitinib treatment (*n*=111) was 6 months (IQR 6–11). Drug survival rates at 6 and 18 months were 73.1% and 48.4%, respectively (Fig. 1A). Drug survival rates for ineffectiveness (*n*=27) were 78.0% and 62.4% at 6 and 18 months, respectively (Fig. 1B). When comparing biologics versus JAKi, we found that discontinuation due to AEs was lower for biologics compared with JAKis. For AEs (*n*=28), the drug survival rates of upadacitinib were 92.4% and 80.1% (Fig. 1C). Abrocitinib (*n*=43) shows slightly lower survival rates compared with upadacitinib. The median overall drug survival was 6 months (IQR 3–7) with overall drug survival rates at 6 and 18 months of 55.8% and 51.5%, respectively (Fig. 1A). Overall drug survival rates for ineffectiveness (*n*=9) were 74.8% at both 6 and 18 months (Fig. 1B) and overall drug survival rates for AEs (*n*=7) were 81.5% and 75.2% (Fig. 1C) at both time points.

Baricitinib treatment (*n*=62) showed the lowest drug survival rates, with a median overall drug survival of 5.5 months (IQR 2–9). At 6 and 18 months drug survival was 54.4% and 20.4%, respectively (Fig. 1A). Drug survival rates due to ineffectiveness were notably lower compared with AEs. For ineffectiveness (*n*=37), the drug survival

Table II. Treatment characteristics of each treatment group in 549 AD patients

	Biologics			JAK inhibitors		
	Total (*n* = 759)	Dupilumab (*n* = 492)	Tralokinumab (*n* = 51)	Abrocitinib (*n* = 43)	Baricitinib (*n* = 62)	Upadacitinib (*n* = 111)
Treatment duration (months), when continued, median [IQR]	16 [6.0–36.8]	27 [13.0–47.0]	5.5 [3.0–12.8]	6.5 [6.0–9.0]	12 [5.3–20.5]	7 [3.0–14.0]
Treatment discontinued, *n* (%)	323 (42.6)	197 (40.0)	23 (45.1)	19 (44.2)	44 (71.0)	40 (36.0)
Treatment duration in months when discontinued, median (IQR)	6 (3.0–14.0)	10 (4.0–24.5)	4 (2.0–7.0)	3 (2.0–5.0)	4 (2.0–7.8)	5 (1.3–7.0)
Reason for discontinuation						
- Ineffectiveness, *n* (%)	184 (24.2)	94 (19.1)	17 (33.3)	9 (20.9)	37 (59.7)	27 (24.3)
- Adverse events, *n* (%)	119 (15.7)	83 (16.8)	6 (11.8)	7 (16.3)	11 (17.7)	28 (25.2)
- Remission, *n* (%)	16 (2.1)	11 (2.2)	0	0	2 (3.2)	3 (2.7)
- Reproductive planning, *n* (%)	15 (2.0)	15 (3.0)	0	0	0	0
- Loss to follow-up, *n* (%)	26 (3.4)	22 (4.5)	1 (2.0)	0	1 (1.6)	2 (1.8)
- Other, *n* (%)	20 (2.6)	12 (2.4)	0	6 (14.0)	1 (1.6)	1 (0.9)
- Missing, *n* (%)	1 (0.1)	1 (0.2)	0	0	0	0
Dose reduction						
- Yes, *n* (%)	149 (19.6)	129 (26.2)	4 (7.8)	5 (11.6)	4 (6.5)	7 (6.3)
- Missing, *n* (%)	7 (0.9)	4 (0.8)	0	2 (4.7)	0	1 (0.9)
Concomitant therapy						
- Yes, *n* (%)	324 (42.7)	292 (59.3)	10 (19.6)	3 (7.0)	10 (16.1)	9 (8.1)
- Cyclosporine A[a], *n* (%)	152 (20.0)	148 (30.1)	2 (3.9)	0	1 (1.6)	1 (0.9)
- Cyclosporine A[b], *n* (%)	17 (2.2)	15 (3.0)	1 (2.0)	0	0	0
- Methotrexate[a], *n* (%)	30 (4.0)	26 (5.3)	1 (2.0)	0	1 (1.6)	2 (1.8)
- Methotrexate[b], *n* (%)	16 (2.1)	11 (2.2)	1 (2.0)	0	3 (4.6)	1 (0.9)
- Azathioprine[a], *n* (%)	11 (1.4)	11 (2.2)	0	0	0	0
- Azathioprine[b], *n* (%)	0	0	0	0	0	0
- Mycophenolic acid[a], *n* (%)	36 (4.7)	36 (7.3)	0	0	0	0
- Mycophenolic acid[b], *n* (%)	0	0	0	0	0	0
- Systemic steroids[a], *n* (%)	79 (10.4)	63 (12.8)	4 (7.8)	3 (7.0)	5 (8.1)	4 (3.6)
- Systemic steroid[b], *n* (%)	2 (0.3)	2 (0.4)	0	0	0	0
- Missing	3 (0.4)	1 (0.2)	0	2 (4.7)	0	0

Patients may have received multiple different treatments over time, resulting in representation across several treatments in the Table (e.g., dupilumab, tralokinumab). Only the initial course of each treatment was included in the analysis, ensuring that each patient was represented only once within each treatment group.
[a]Dose of conventional systemic is gradually reduced until discontinuation in the first 3 months of treatment with an advanced systemic. [b]Dose of conventional systemic is reduced during treatment with advanced systemic, but not discontinued.
n: number of treatment courses; AD: atopic dermatitis; IQR: interquartile range.

rates were 63.0% and 24.7% at 6 and 18 months (Fig. 1B), whereas for AEs (*n* = 28), drug survival was 83.9% and 67.6%, respectively (Fig. 1C).

Discontinuation of treatment

In total, 197/492 dupilumab treatment courses (40.0%) were discontinued, including 19.1% due to ineffectiveness and 16.8% due to AEs. For tralokinumab, 23/51 treatment courses (45.1%) were discontinued, mainly due to ineffectiveness (33.3%) (Table II). The most common AEs reported for dupilumab discontinuation were conjunctivitis (53.8%) and head and neck dermatitis (15.2%). Notably, conjunctivitis was less frequently reported as a reason for discontinuation in tralokinumab patients compared with dupilumab patients (66.7% vs 85.6%).

For JAKi, 40/111 upadacitinib courses (44.4%) and 19/43 abrocitinib courses (44.2%) were discontinued, including 24.3% and 20.9% due to ineffectiveness, respectively. For AEs, 25.3% of upadacitinib and 16.3% of abrocitinib courses were discontinued, most commonly due to upper respiratory tract infection, acne, and headache (Table II). Baricitinib was discontinued in 44/62 cases (71.0%), primarily due to ineffectiveness (59.7%). See Table SI for AEs leading to discontinuation by treatment group.

Predictors of treatment discontinuation

Age of treatment initiation, gender, Fitzpatrick skin types, and a history of using 3 or more immunosuppressive treatments were investigated as potential predictors of drug survival. This study did not identify any significant predictors of treatment discontinuation. Detailed results are provided in Appendix S2.

The AD treatment landscape

As itemized in **Table III**, 147/549 (26.8%) patients switched from a first to a second advanced systemic, 50 (9.1%) from a second to a third, and 10 (1.8%) to a fourth. Dupilumab was the most frequently prescribed initial treatment (*n* = 479, 87.2%). Among patients who switched treatments, 71.3% switched to a JAKi as a second treatment, with upadacitinib being the most frequent second (*n* = 50, 34.0%) and third (*n* = 28, 56.0%) treatment. Fig. S2 shows initial to second treatment patterns, indicating that patients starting on baricitinib had the highest switching rate (73.0%).

A Sankey diagram (**Fig. 2**) visually represents treatment trajectories over time, showing that 57.9% of patients remained on their initial treatment during follow-up, 15.3% discontinued their initial treatment (defined as discontinuation of a treatment and not restarting

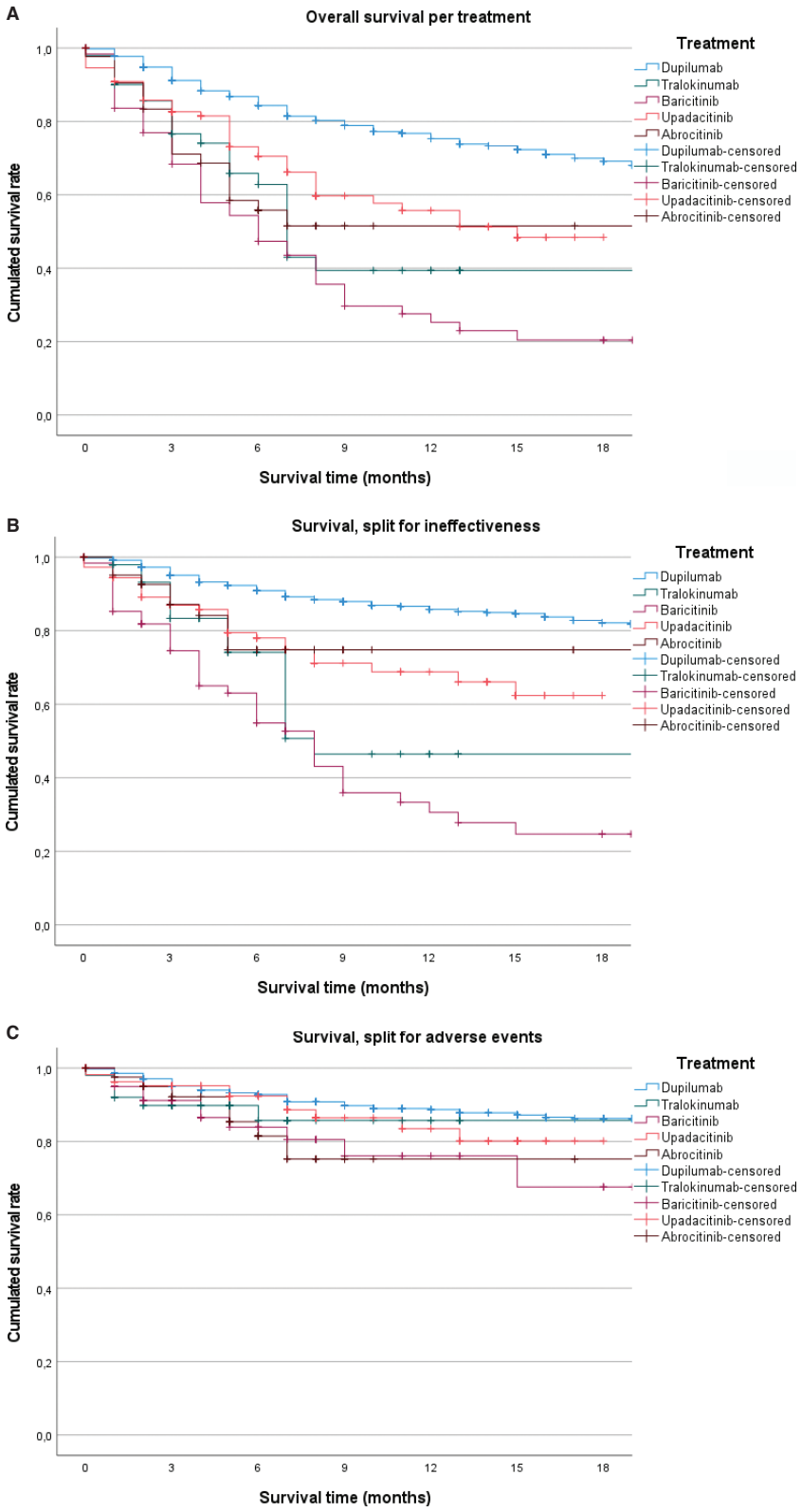

Fig. 1. Kaplan–Meier survival curves with the cumulative survival per treatment: (A) Overall survival, (B) split for ineffectiveness, (C) split for adverse events. (A): 18-month drug survival of dupilumab, tralokinumab, baricitinib, upadacitinib, and abrocitinib in 549 AD patients. *n* = 759 treatment courses. Event = overall discontinuation of treatment. Dupilumab shows the most favourable drug survival. Baricitinib has the lowest overall drug survival rate. (B) 18-month drug survival, split for ineffectiveness, of dupilumab, tralokinumab, baricitinib, upadacitinib, and abrocitinib in 549 AD patients. *n* = 759 treatment courses. Event = discontinuation of treatment due to ineffectiveness. Dupilumab shows the most favourable drug survival months. Baricitinib has the lowest drug survival rate. (C) 18-month drug survival, split for adverse events, of dupilumab, tralokinumab, baricitinib, upadacitinib, and abrocitinib in 549 AD patients. *n* = 759 treatment courses. Event = discontinuation of treatment due to adverse events. There is a trend towards better drug survival with the biologics (dupilumab and tralokinumab) compared with the JAK inhibitors (upadacitinib, abrocitinib, baricitinib).

Table III. Treatment patterns from initial and subsequent treatments in atopic dermatitis ($n = 549$)

	Treatments, *n* (%)			
New systemic treatment	Initial treatment	Second treatment	Third treatment	Fourth treatment
Total	549 (100.0)	147 (26.8)	50 (9.1)	10 (1.8)
Dupilumab	479 (87.2)	12 (8.2)	1 (2.0)	0
Tralokinumab	7 (1.3)	30 (20.4)	9 (18.0)	4 (40.0)
Abrocitinib	5 (0.9)	23 (15.6)	11 (22.0)	3 (30.0)
Baricitinib	29 (5.3)	32 (21.8)	1 (2.0)	0
Upadacitinib	29 (5.3)	50 (34.0)	28 (56.0)	3 (40.0)

any systemic treatment during follow-up), and 26.8% switched to a second advanced systemic treatment. The diagram highlights that while dupilumab is the preferred initial treatment, many patients switch to alternative treatments over time. The decreasing number across successful treatment stages suggest that most patients eventually find an effective treatment.

DISCUSSION

In this study, we aimed to explore real-world therapeutic responses to new systemic treatments for AD by conducting drug survival analyses and studying treatment patterns. Dupilumab treatment was shown to have the highest survival rate in terms of both effectiveness and safety, whereas baricitinib had the lowest survival rate and treatment was mostly discontinued due to ineffectiveness. Dupilumab was the first biologic registered in the Netherlands (15). In the current cohort, most patients started dupilumab as their initial advanced systemic, potentially resulting in bias as patients who have previously been treated with other new systemics may have more difficult-to-treat AD. This may have a negative impact on the drug survival outcomes of treatments started after dupilumab. In addition, previous systemic treatment has been identified as a predictor for lower drug survival in studies of biologics for AD and psoriasis (8, 16). Furthermore, in the Netherlands, there are no strict guidelines for switching to alternative treatments, such as achieving an Eczema Area and Severity Index (EASI) 50 after a specific treatment period. As a result, patients may continue treatment for fear of switching to potentially more effective treatments, a phenomenon known as conservatism bias (17). This may affect the drug survival outcomes in our cohort. However, our cohort provides insights into real-world treatment patterns, which may be similar across countries due to harmonized drug approval dates.

In our study, overall drug survival after 18 months of treatment with dupilumab was 70.3%, slightly lower than recent studies reporting 2-year survival rates between 85.9% and 89.0% (8, 18). In these studies, the lack of alternative new systemic treatments and therefore the

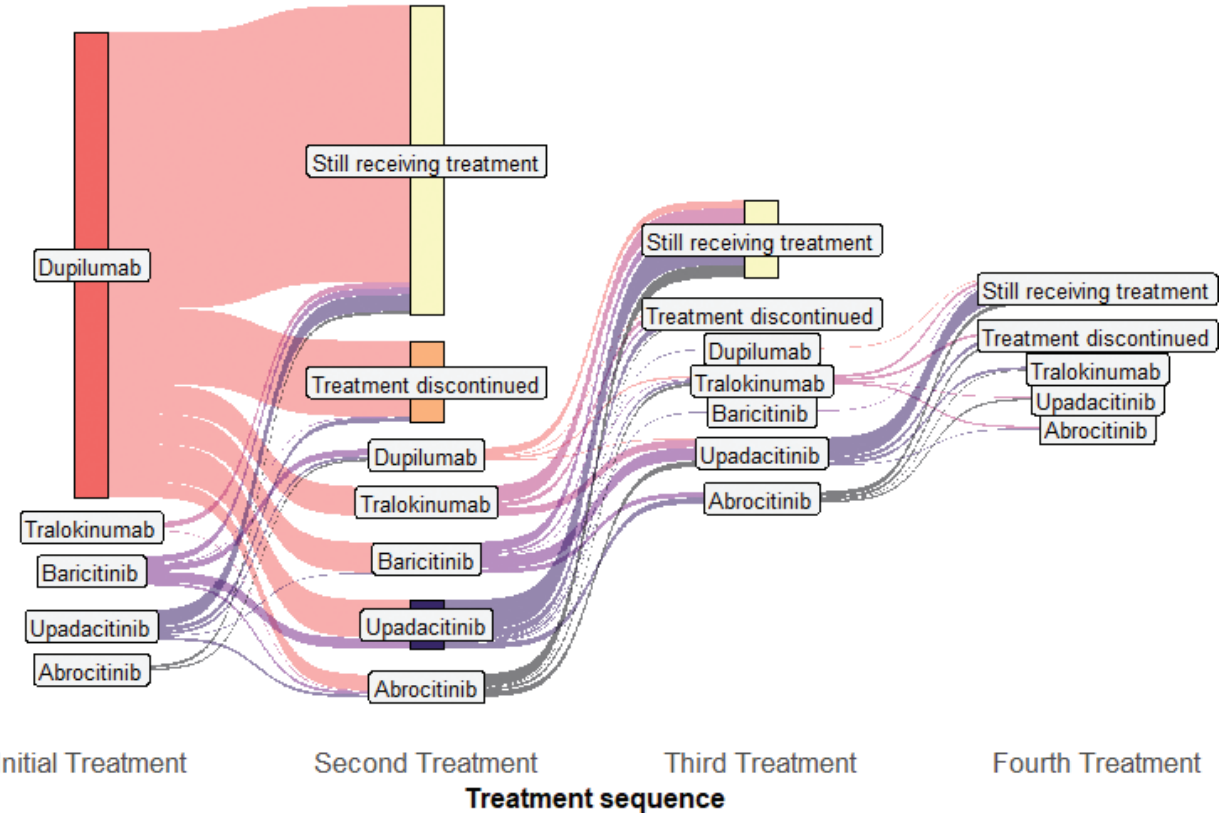

Fig. 2. Treatment patterns of the new systemic treatments. Treatment sequence indicates the order of treatment. The Sankey diagram shows that dupilumab is the predominant regimen in first-line treatment. Upadacitinib is the most common second and third treatment.

unavailability of switching options may explain higher survival rates compared with our study. Baricitinib was found to have the lowest drug survival of all JAKi and had the highest rate of switchers. Baricitinib treatment was mostly discontinued due to its lack of efficacy. The high rate of transitioning from baricitinib to the other JAKi and lower drug survival may be explained by meta-analyses that suggest better efficacy of upadacitinib and abrocitinib compared with baricitinib (19).

Although adherence to the initial advanced systemic was 57.9%, 27% of patients switched to another treatment with most patients switching from a biologic to a JAKi. This shows that there is an important unmet need in predicting response to advanced systemics. Some 26.8% of the patients in this cohort are exposed to (expensive) drugs that prove to be unsuccessful after a median treatment period ranging from 3 to 10 months. In these patients, switching from biologics to JAKi and vice versa can be successful. We did not identify any predictors for treatment discontinuation in this study. In future studies, predictors such as disease severity scores, and serum or tissue biomarkers, may be useful predictors of treatment (dis)continuation. It is important to note patients were included between 2017 and 2023, a period in which several new treatments for AD became available (Fig. S1). Factors such as the time of registration of new treatments, and physicians' experience with these new treatments, may have influenced the results described in this study.

The introduction of biologics and JAKi for AD and many other diseases has large effects on healthcare costs. Reduction of costs by increasing the interval of biologics may help to control these costs (20). In our cohort, we found that in 26.2% of dupilumab courses, dose reduction by extending the interval between doses was successful. This is consistent with previous findings demonstrating the success of dose reduction by using patient-centred dosing regimens in controlled AD (21). Future research should explore tralokinumab and JAKi dosing regimens and conduct economic evaluations to enhance patient access to these new systemic treatments for AD.

Ocular AEs were the most frequently reported AEs leading to discontinuation of dupilumab treatment in this study. Interestingly, ocular AEs are less common in patients treated with tralokinumab. This is consistent with findings reported in previous clinical trials and daily practice studies with incidence rates of up to 62.0% with dupilumab and up to 24.0% with tralokinumab treatment (2, 10, 13, 22–32). Ensuring effective management of ocular AEs during dupilumab and tralokinumab treatment may have influence on the overall drug survival (33). Furthermore, survival analyses show a lower survival rate for AEs with JAKi compared with biologics in this study. Commonly reported AEs of JAKi include upper respiratory tract infection, nasopharyngitis, headache, herpes simplex, and acne. This is in line with previous studies (6, 34, 35). Safety concerns, including the risk of major adverse cardiovascular events (MACE), have recently emerged from studies of tofacitinib in rheumatoid arthritis (RA) patients, prompting a boxed warning from the Food and Drug Administration (FDA) in 2019 (36). No cases of MACE were reported in our study, possibly due to a different patient population profile (younger patients and with fewer comorbidities and fewer co-medications compared with RA patients).

The strengths of this study include the relatively large number of patients included from our prospective registry. However, several limitations should be considered. This study was performed in a large academic hospital in the Netherlands. Different regulations (e.g., reimbursement regulations) may apply in different countries resulting in different treatment patterns. In our centre, there has been no preference (due to, e.g., lower costs) for a specific advanced treatment, which is unique compared with most other centres and countries.

In addition to these potential limitations, dupilumab was the first and only treatment available for several years. The majority of dupilumab treatments (61.2%) in this study were initiated between 2017 and 2020. In these initial years it was therefore not possible to switch to other new systemics, potentially leading to higher drug survival rates for dupilumab compared with the other advanced systemics. In addition, differences in sample sizes for the different treatments may have influenced the observed variations in treatment survival. However, the introduction of several new drugs in a relatively short period of time may also have encouraged clinicians and patients to switch treatments. Another limitation is that a subset of patients continued low doses of conventional systemic immunosuppressants while on biologic treatment, which may lead to a slight overestimation of drug survival for these drugs. However, this reflects real-world treatment.

In conclusion, dupilumab appears to have the most favourable drug survival in terms of effectiveness and safety and was the most frequently prescribed initial treatment. The high frequency of switching between new advance systemics highlights the importance of identifying predictors of treatment response.

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