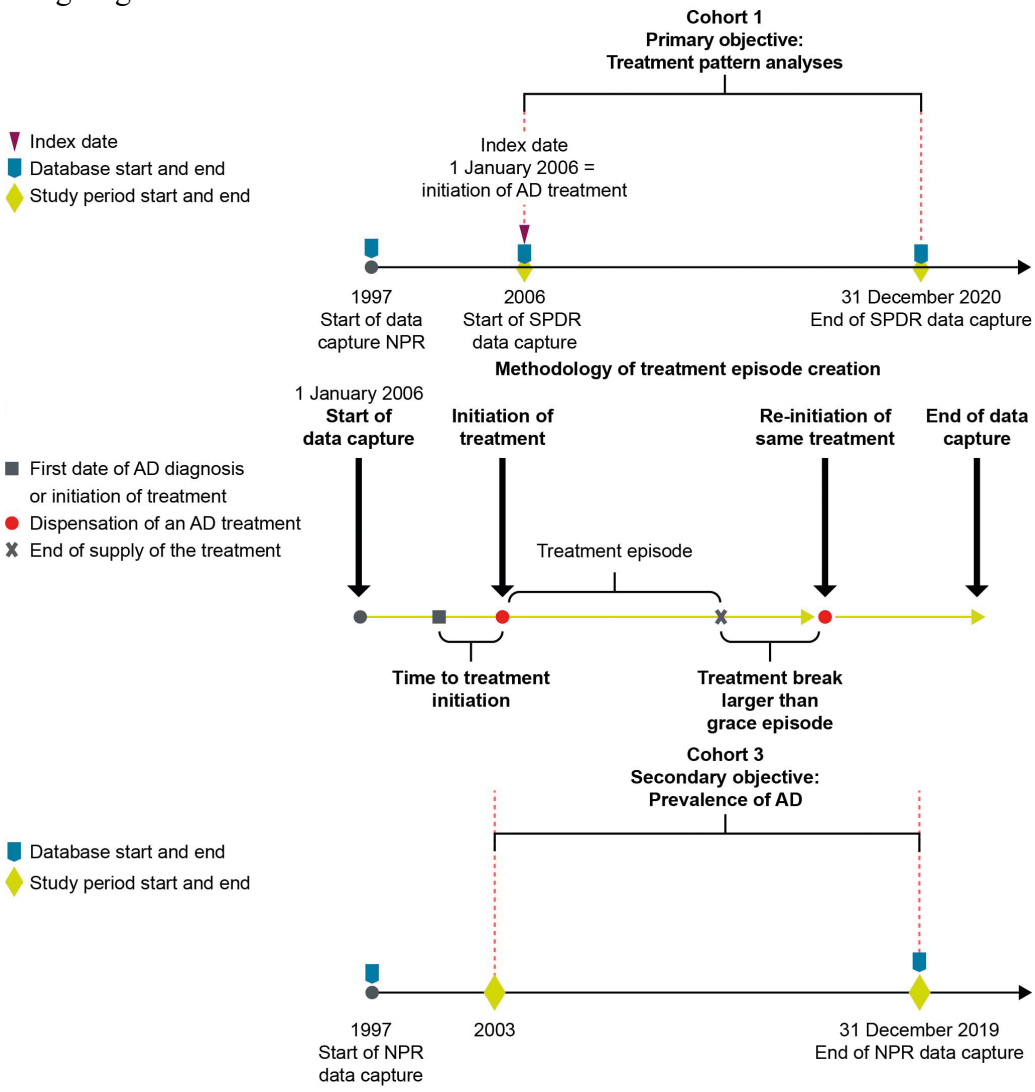
Appendix S1
SUPPLEMENTARY METHODS.

Study design: Description of the cohorts

Patients with AD as primary or secondary diagnosis for a secondary care visit in Sweden during 1 January 2003 to 31 December 2019 were identified and referred to as cohort 3 (Fig. S1); this population was used to estimate the 12-month prevalence. As the collection of data into the outpatient register (NPR) started in 2001, patients were followed from January 2003 to avoid a steep increase in the prevalence of AD in the earlier years of the study period.

To select a population with higher ascertainment of AD and active treatment, patients with ≥2 AD diagnoses as a main diagnosis recorded in the NPR that were prevalent on 1 January 2003 (i.e. previously diagnosed patients with AD who were alive on 1 January 2003 or newly diagnosed patients with AD on or after 1 January 2003) *and* AD treatment dispensed as recorded in the SPDR between 1 January 2006 and 31 December 2020 were selected, referred to as cohort 1 (Fig. S1). Patients with at least 1 dispensation of systemic treatment specifically were selected and referred to as cohort 2. In cohorts 1 and 2, patients were followed from January 2006, since this is when the first full year of data in the SPDR is available. However, the AD diagnosis could be much earlier, as the data capture for the NPR in this study started as early as January 1997.

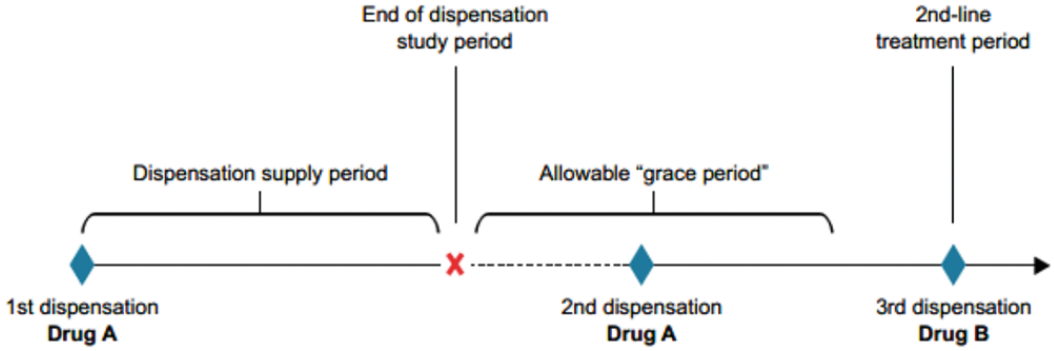
Fig. S1. Study design. AD: atopic dermatitis; NPR: National Patient Register; SDPR: Swedish Prescribed Drug Register.



Grace period: rationale and methods

In this study, drug persistence was defined as the duration of time from dispensation to discontinuation of therapy. Treatment persistence was calculated from the date of first dispensation to the date of discontinuation of the treatment being considered. The discontinuation of treatment was defined as the end of the supply of the last dispensation (i.e. date of last dispensation plus days supplied during last dispensation). A treatment break was determined if a patient had not been dispensed a specified treatment for a given period, but reinitiated the same treatment (**Fig. S2**). Thus, delays in dispensation pick-ups are accounted for. The permitted time for a treatment break is called the allowable "grace period". If the next dispensation of the same treatment occurred within the allowable "grace period", then the treatment was determined to have been continued. However, if the next dispensation occurred after the allowable "grace period", then the treatment was determined to have been discontinued; from this point, a new treatment period was initiated.

Fig. S2. Overview of the allowable "grace period".



An individual patient could receive several dispensations with different durations for a given drug. Thus, consecutive treatments are merged, unless the patient took a treatment break longer than the allowable "grace period." The first line of each treatment ended at the date of treatment discontinuation. If the patient reinitiated the same treatment with a gap longer than the grace period, they were determined as being on the second treatment line of that agent. If the same treatment was reinitiated after the "grace period," only the first treatment episode of each respective immunomodulatory agent or biological was analysed for persistence in this study.

The length of the "grace period" for topical treatments was determined to be 1 year (365 days). Patients receiving a dispensation of a topical treatment on a yearly basis may be assumed to be on continuous treatment for the given topical drug. A feasibility analysis of time between dispensations of topical treatments was performed to assess the best "grace period" for those treatments. The length of the "grace period" for all other treatments was decided after exploring how the share of patients reinitiating the same treatment varied with different "grace period" options (e.g. 60, 90, 120 days).

The persistence analysis was additionally stratified by healthcare region and drug types.

Kaplan–Meier methodology

Survival analyses were used to analyse treatment persistence of AD treatments (S1). In all the drug persistence analyses, unadjusted estimates of drug persistence (i.e. risk tables) were reported per month for each therapy. Output from the persistence analyses include the number and percentage of patients still at risk after a pre-specified period. The persistence probability at time t_i, $S(t_i)$ was calculated as follows:

$$S(t_i) = S(t_{i-1})\,(1 - \frac{d_1}{n_1})$$

Where $S(t_{i-1})$ is the probability of being still on a treatment at t_{i-1}, n_i is the number of patients alive just before t_i, d_i is the number of events at t_i, and t_0=0, $S(0)$=1. However, the event (discontinuation of treatment) may not have been observed for some individuals during the study time-period, producing the censored observations. When Kaplan–Meier methodology was applied in the persistence analysis context, $S(t_{i-1})$ is the probability of being on treatment at t_{i-1}, n_i is the number of patients being on treatment just before t_i, d_i is the number of discontinuations (events) at t_i, and t_0=0, $S(0)$=1.

Discontinuations were recorded if the patient switched to another drug or received no dispensations after the grace period. An observation was censored if the last registration of dispensed treatment continued in the last months of the data cut, or the patient died. Results are displayed on a persistence curve.

Estimation of 12-month prevalence

The prevalence of atopic dermatitis was calculated per calendar year using the method below:

$$Prevalence_{year,subgroup} = \frac{\#\ of\ all\ AD\ patients_{year,subgroup}}{Total\ population_{year,subgroup}} \times 10^{n}$$

The numerator is the number of all AD cases within the given calendar year; this includes newly and previously diagnosed patients. In the analysis of prevalence patients who died during the follow-up were excluded. The denominator considers the Swedish population within the given calendar year.

Swedish healthcare regions (Table SI)

Table SI. Counties included in each stratified region

Region		Counties
Stockholm (SLL)		Stockholm County
		Gotland County
South (Skåne)		Skåne County
		Blekinge County
		Kronoberg County
		Halland County (3 of 6 municipalities)
West (VGR)		Västra Götaland County
		Halland County (3 of 6 municipalities)
Other	Uppsala-Örebrö (7-klövern)	Södermanland County
		Örebrö County
		Värmland County
		Västmanland County
		Uppsala County
		Dalarna County
		Gävleborg County
	North (Norrland)	Norrbotten County
		Västerbotten County
		Västernorrland County
		Jämtland County
	South-East (Sydöstra)	Kalmar County
		Jönköping County
		Östergötland County

SUPPLEMENTARY RESULTS

Demographics and disease characteristics (**Table SII**)

Table SII. Demographics and disease characteristics

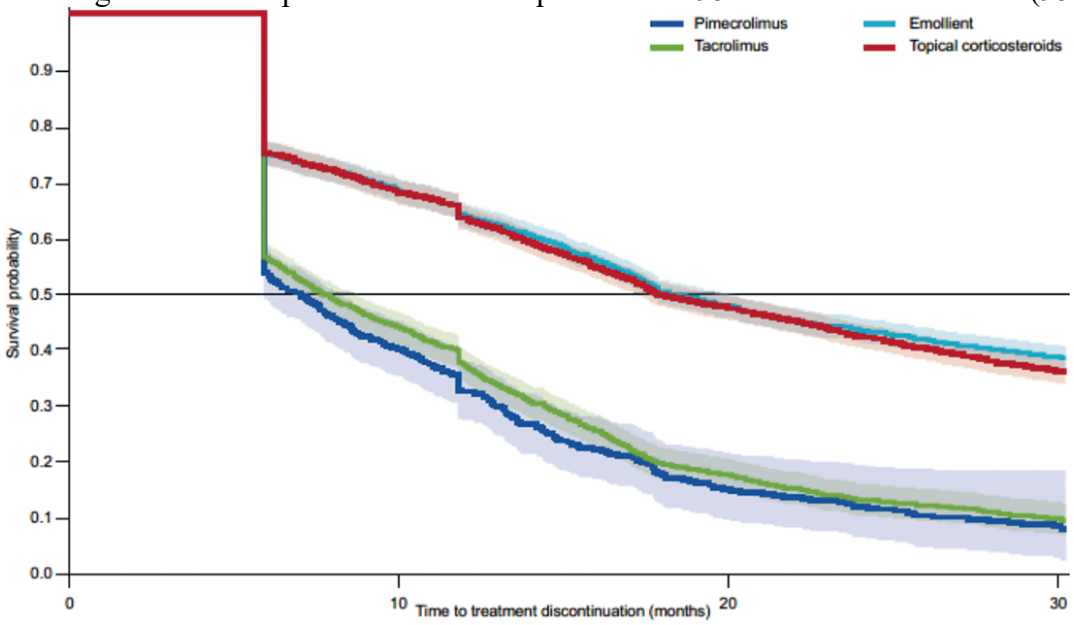
Cohort[a]	N	Age at diagnosis (years)			Sex, *n* (%)	
		Mean	Median (LQ, UQ)	Range	Male	Female
Cohort 1	99,885	15.3	7 (1, 24)	0–97	44,574 (44.6)	55,311 (55.4)
Cohort 2	4,086	33.89	32 (17, 50)	0–92	1,782 (43.6)	2,304 (56.4)
Cohort 3	300,534	15.8	7 (1, 24)	0–108	139,725 (46.5)	160,809 (53.5)

[a]Cohort 1 included patients who had ≥2 AD main or secondary diagnoses and treatment; cohort 2 included patients with AD who had ≥1 episode of systemic treatment; cohort 3 included patients who had ≥1 main or secondary diagnosis of AD between January 2003 and December 2019.
AD: atopic dermatitis; LQ: lower quartile; UQ: upper quartile.

Treatment persistence of topical treatments

Of all treatments included in the study (systemic and topical), emollients had the highest treatment persistence (median 18.1 months). Topical corticosteroids also had a relatively long treatment persistence (median 17.9 months). Drug persistence for topical treatments is shown in **Fig. S3**. Similar treatment persistence was observed by region (Table III) to that of the overall population (Table II) for all topical treatments. Topical corticosteroids and emollients were the most commonly used topical treatments across all age groups (Table III). Treatment persistence was longest on emollients for infants and adults (median 32.8 and 20.3 months, respectively), with children and adolescents demonstrating longest treatment persistence on topical corticosteroids (median 15.5 and 114.9 months, respectively).

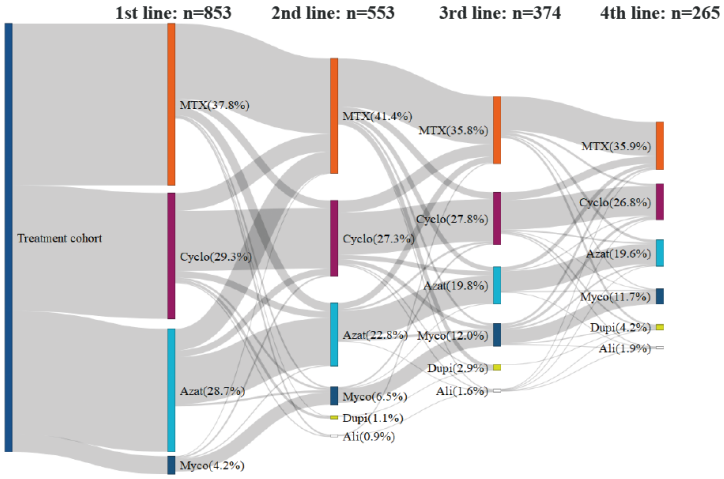
Fig. S3. Kaplan–Meier plot for treatment persistence of topical treatments for all patients in cohort 1. Shading around each persistence curve represents the 95% confidence intervals (95% CI).



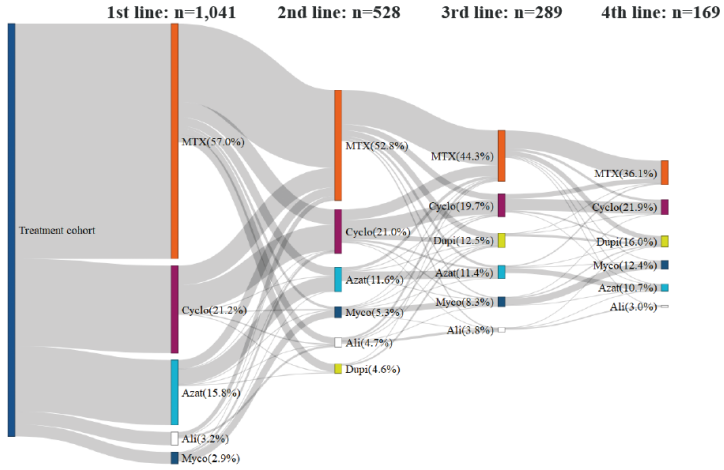
Treatment sequences

Fig. S4. Sankey plots showing treatment sequence after initiation of first systemic treatments over different time-periods. *n*: number of patients for each treatment sequence. Ali: alitretinoin; Azat: azathioprine; Cyclo: cyclosporine; Dupi: dupilumab; MTX: methotrexate; Myco: mycophenolate mofetil. (a) Time-period: 1 January 2006 to 31 December 2009. (b) Time-period: 1 January 2010 to 31 December 2014. (c) Time-period: 1 January 2015 to 31 December 2020.

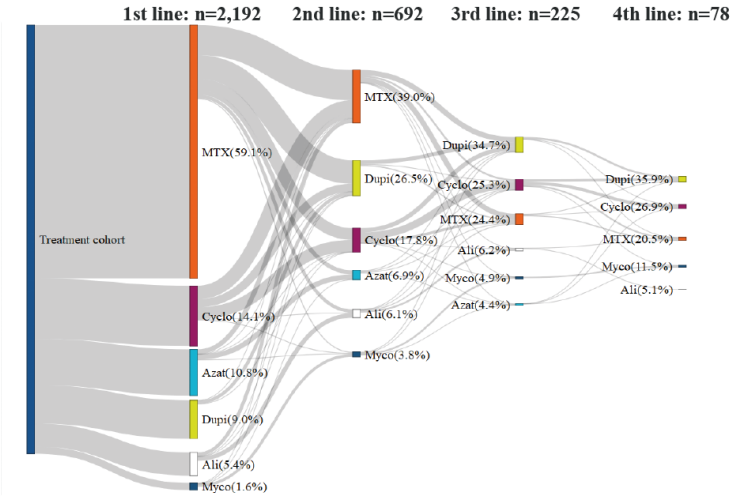
1. Time period: 1 January 2006 to 31 December 2009



2. Time period: 1 January 2010 to 31 December 2014



3. Time period: 1 January 2015 to 31 December 2020



REFERENCE

S1. Bland JM, Altman DG. Survival probabilities (the Kaplan-Meier method). BMJ 1998; 317: 1572.