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Systemic lupus erythematosus

Reduced organ damage accumulation in adult patients with SLE on anifrolumab plus standard of care compared to real-world external controls

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ABSTRACT

Objectives: Anifrolumab is approved for the treatment of systemic lupus erythematosus (SLE). We aimed to determine if anifrolumab plus standard of care (SOC) was associated with reduced organ damage accumulation in adult patients with moderately to severely active SLE compared to real-world (RW) external controls from the University of Toronto Lupus Clinic (UTLC) cohort who received SOC only.

Methods: Patients who initiated 300 mg anifrolumab in the TULIP (Treatment of Uncontrolled Lupus via the Interferon Pathway) trials were included in the anifrolumab arm; key eligibility criteria were applied to the UTLC to create the RW SOC arm. Propensity score and censoring weighting were used to account for baseline confounding and loss to follow-up. The primary endpoint was change in Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) score from baseline to week 208, and the secondary endpoint was time to first SDI score increase.

Results: 354 patients were included in the anifrolumab arm, and 561 patients were included in the RW SOC arm. Following weighting, mean change in SDI was 0.416 points lower (95% CI: −0.582, −0.249; $P < .001$) in the anifrolumab arm than in the RW SOC arm. Patients in the anifrolumab arm were 59.9% less likely (hazard ratio: 0.401; 95% CI: 0.213, 0.753, $P = .005$) to experience an increase in SDI within 208 weeks.

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Conclusions: Patients who received anifrolumab accumulated significantly less organ damage after 208 weeks than patients who received RW SOC. The addition of anifrolumab to SOC is effective at preventing and/or delaying organ damage in patients with moderately to severely active SLE.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Patients with systemic lupus erythematosus (SLE) typically accumulate irreversible organ damage due to uncontrolled disease activity, disease flares, and long-term glucocorticoid treatment.
- The accumulation of organ damage is associated with multimorbidity, increased health care costs, and increased mortality.
- Anifrolumab has previously been demonstrated to be effective for controlling disease activity while simultaneously reducing the dose of glucocorticoids; however, its long-term effectiveness for preventing organ damage requires further elucidation.

WHAT THIS STUDY ADDS

- This study demonstrates that anifrolumab plus standard of care (SOC) is effective at reducing organ damage accumulation and prolonging time to organ damage progression compared to SOC alone over 4 years.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- These results support the use of anifrolumab plus SOC as a safe and effective long-term treatment for SLE, which may assist clinicians in determining the appropriate treatment for patients with SLE.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease that can lead to widespread inflammation and tissue damage in the affected organs [1]. Treatment for SLE aims to achieve remission or low disease activity and prevention of disease flares. Conventional standard of care (SOC) consists primarily of antimalarials, glucocorticoids, immunosuppressants, and nonsteroidal anti-inflammatory drugs [2]. However, numerous studies have demonstrated that irreversible organ damage accrual in SLE is linked to uncontrolled disease activity, disease flares, and long-term glucocorticoid treatment [3–5]. Early diagnosis and treatment with advanced therapies to reduce disease activity and reliance on glucocorticoids is recommended to prevent organ damage accrual in patients with SLE [6].

Type 1 interferons (T1IFNs) play an important role in the pathogenesis of SLE, and T1IFN antagonists have demonstrated efficacy for the treatment of SLE [7,8]. Anifrolumab is a human immunoglobulin G1 kappa monoclonal antibody that inhibits the biologic activity of T1IFNs by binding to the common T1IFN receptor. Anifrolumab has been evaluated in 2 separate 52-week phase 3, randomised, double-blind trials known as the TULIP (Treatment of Uncontrolled Lupus via the Interferon Pathway) trials (ClinicalTrials.gov identifiers: NCT02446912 and NCT02446899) [9,10]. In TULIP-2, the efficacy of anifrolumab compared to placebo after 1 year of treatment was demonstrated using the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) response criterion, in patients with moderate to severely active SLE receiving SOC treatment [8,11]; these findings were supported by TULIP-1 [12]. A 3-year long-term extension (LTE) of the trials also supported the long-term safety, tolerability, and efficacy of anifrolumab (ClinicalTrials.gov identifier: NCT02794285) [13,14]. Anifrolumab has been approved for use in over 50 countries, including United States, Europe, Canada, Australia, and Japan [15–17].

Although anifrolumab has been shown to reduce disease activity and promote reduction of glucocorticoids [14,18,19], its long-term effectiveness for preventing organ damage compared to SOC requires further elucidation. Patients who received placebo in TULIP-1 or -2 were randomised at a 4:1 ratio to switch to anifrolumab plus SOC in the LTE study, and there was a high dropout rate in the placebo arm. Of the 368 patients allocated to the placebo arm in TULIP-1 or -2, 270 (73.4%) completed the initial year-long study, and only 54 (14.7%) completed the LTE study while still receiving placebo. In comparison, 361 patients were allocated to receive 300 mg of anifrolumab in TULIP-1 or -2, 296 (82.0%) completed the initial year-long study, and 178 (49.3%) completed the LTE study while still receiving anifrolumab [8,18,19]. Previous analyses found that mean Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) score remained stable across treatment arms in the LTE study [14]. However, the high attrition rate in the placebo arm and the discrepancy in completion rates across arms prevented accurate analysis of the long-term impact of anifrolumab on damage accrual directly in the trial dataset, resulting in the need for alternative forms of evidence generation. It is also of interest to understand how changes in organ damage observed in the TULIP trials among patients who received anifrolumab compared to real-world (RW) evidence.

In this study, we estimated the effectiveness of anifrolumab on preventing organ damage over 4 years in adult patients with moderately to severely active SLE using a RW external control arm from the University of Toronto Lupus Clinic (UTLC). We also estimated the effectiveness of anifrolumab on prolonging time to organ damage progression.

METHODS

Study design

This was a retrospective study that compared patients who initiated 300 mg of anifrolumab while receiving stable SOC treatment in TULIP-1 and -2 (ie, the 'anifrolumab arm') to external controls in the UTLC who received RW SOC (ie, the 'RW SOC arm').

Patients in the anifrolumab arm were indexed at anifrolumab initiation and were followed until the earliest of death, loss to follow-up, or week 208 assessment in the LTE study. Patients in the RW SOC arm were indexed at the first instance of meeting all eligibility criteria in which they were receiving ≥1 eligible SOC treatment (their 'index assessment') between January 1, 1995, and December 31, 2023 [20]; they were followed until the earliest of death, loss to follow-up, or December 31, 2023.

Data sources

This study used data from the TULIP trials (-1, -2, and LTE) and from the UTLC. The TULIP trials were conducted between

2015 and 2021. TULIP-1 evaluated the efficacy and safety of 2 doses of anifrolumab (150 mg and 300 mg) vs placebo [9], while TULIP-2 evaluated the efficacy and safety of 300 mg of anifrolumab vs placebo [10], both after 52 weeks of treatment. Patients who initiated 300 mg of anifrolumab in TULIP-1 or -2 were able to continue receiving treatment in the LTE study for up to 156 additional weeks (ie, 3 years) [13]. Across all trials, patients were assessed every 4 weeks according to a standardised protocol that included demographic, clinical, laboratory, and treatment measurements.

The UTLC was established in 1970 in Toronto, Ontario, Canada and has since enrolled patients with SLE as part of a prospective cohort study [21]. Patients are typically assessed every 3 to 4 months according to a standardised protocol that includes demographic, clinical, laboratory, and treatment measurements.

Patient selection

All eligible patients who initiated 300 mg of anifrolumab in TULIP-1 or -2 were included in the anifrolumab arm (regardless of subsequent enrolment in the LTE study). Patients in the UTLC were included in the RW SOC arm if they met key eligibility criteria from TULIP-1 and -2. Inclusion criteria (evaluated at index) were: aged 18 to 70; weight ≥40.0 kg; diagnosis of SLE ≥24 weeks prior using ≥4 of the 11 modified American College of Rheumatology classification criteria, with ≥1 positive antinuclear antibody test, anti-dsDNA antibodies, or elevated anti-Smith antibody; Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) ≥6 points; no record of current pregnancy; and valid measurement of SDI score. Exclusion criteria (evaluated at index) were: glucocorticoid dose >40 mg/d (oral prednisone equivalent); current receipt of any biologic agent or within 4 weeks prior; record of prior malignancy, except skin malignancy ≥1 year prior; record of persistent, new, or recurrent nephrotic syndrome, chronic dialysis, or renal transplant; or serum creatinine >2.0 mg/dL.

Treatment strategies

The active exposure was 300 mg of anifrolumab, delivered intravenously every 4 weeks, in combination with SOC. Eligible SOC included glucocorticoids, antimalarials, and immunosuppressants. Patients were not allowed to initiate new antimalarials or immunosuppressants, and dosage was required to remain stable through week 52. Between weeks 8 to 40, glucocorticoid dose tapering to ≤7.5 mg/d was attempted in all patients with a baseline dose of ≥10 mg/d.

The comparison exposure was RW SOC, delivered according to standard clinical practice in the UTLC. Eligible SOC included glucocorticoids, antimalarials, and immunosuppressants, without restriction on dosage or length of treatment.

Outcomes

We used SDI score to assess irreversible damage across 12 organ systems. SDI is a validated measure that has been used in clinical trials and RWD analyses [3,21–23]; its score can range from 0 to 46 points [24]. In TULIP-1 and -2, SDI was assessed at weeks 0, 24, and 52; in the LTE study, SDI was assessed at weeks 104, 156, and 208. In the UTLC, SDI has been assessed prospectively on an annual basis since 1995 [21].

The primary study endpoint was change in SDI from index date to week 208. The value of SDI at week 208 was derived in study participants with ≥208 weeks of follow-up. For patients in the anifrolumab arm, SDI at week 208 was used if available; otherwise, since SDI values cannot decrease over time, its value was imputed by carrying forward the most recently recorded value. For patients in the RW SOC arm, SDI at week 208 was used if available; otherwise, its value was imputed using linear interpolation from the closest values recorded before and after. For study participants with <208 weeks of follow-up, SDI at week 208 was considered missing due to loss to follow-up.

The secondary study endpoint was time to first SDI progression, defined as the time from index date to the first observed increase in SDI.

Baseline and confounding variables

Operational definitions of variables were harmonised across the TULIP trials and UTLC. In TULIP, baseline characteristics were recorded at randomisation or during a screening visit within 30 days before randomisation. In UTLC, baseline characteristics were recorded at the initial assessment performed upon enrolment or during the index assessment.

Baseline confounders were selected following consultation with clinical experts and a relevant study [22]. The following characteristics (evaluated at index) were considered: age; SLE duration (y); gender (as recorded); race; SLEDAI-2K score; SDI score; proteinuria; glucocorticoid use; glucocorticoid dose (mg/d, oral prednisone equivalent); antimalarial use; immunosuppressant use; high blood pressure (BP) or hypertension; and history of smoking.

The following baseline variables were also described: year of diagnosis; age at diagnosis; year of index; body mass index (BMI) at index; and serum creatinine level at index (mg/dL).

Statistical analysis

Baseline variables were described stratified by treatment arm. Continuous variables were described as mean (SD) and median (Q1, Q3), and categorical variables were described as counts and percentages. After assessing missingness patterns, missing values for baseline confounders were imputed using a 2-stage approach. First, where available, values recorded within 3 months before or after index were used for direct imputation, followed by multiple imputation.

Comparative analyses estimated the relative average treatment effect of initiating 300 mg of anifrolumab plus SOC compared to receiving RW SOC. To allow the estimated treatment effect to be generalisable to patients represented by the RW SOC arm, the average treatment effect in the control (ATC) was chosen as the primary estimand. Standardised mortality ratio weighting (SMRW) based on propensity scores was used to adjust for baseline confounding [25,26]. Standardised mean differences (SMDs) were used to assess baseline imbalance before and after SMRW [27,28]. Inverse probability of censoring weighting (IPCW) was used to account for possibly informative loss to follow-up [29].

Mean change in SDI from index to week 208 was calculated separately in each weighted treatment arm. The mean difference in change in SDI from index to week 208 between the anifrolumab and RW SOC arms was then estimated using a weighted linear regression model, which was additionally adjusted for variables that remained imbalanced (SMD ≥0.2) after SMRW. The point estimate and corresponding 95% CI and *P* value were estimated. As sensitivity analyses, the average treatment effect in the treated (ATT) was estimated using the same methods, and the average treatment effect in the overlap (ATO) population was estimated using 1:1 nearest-neighbour matching with

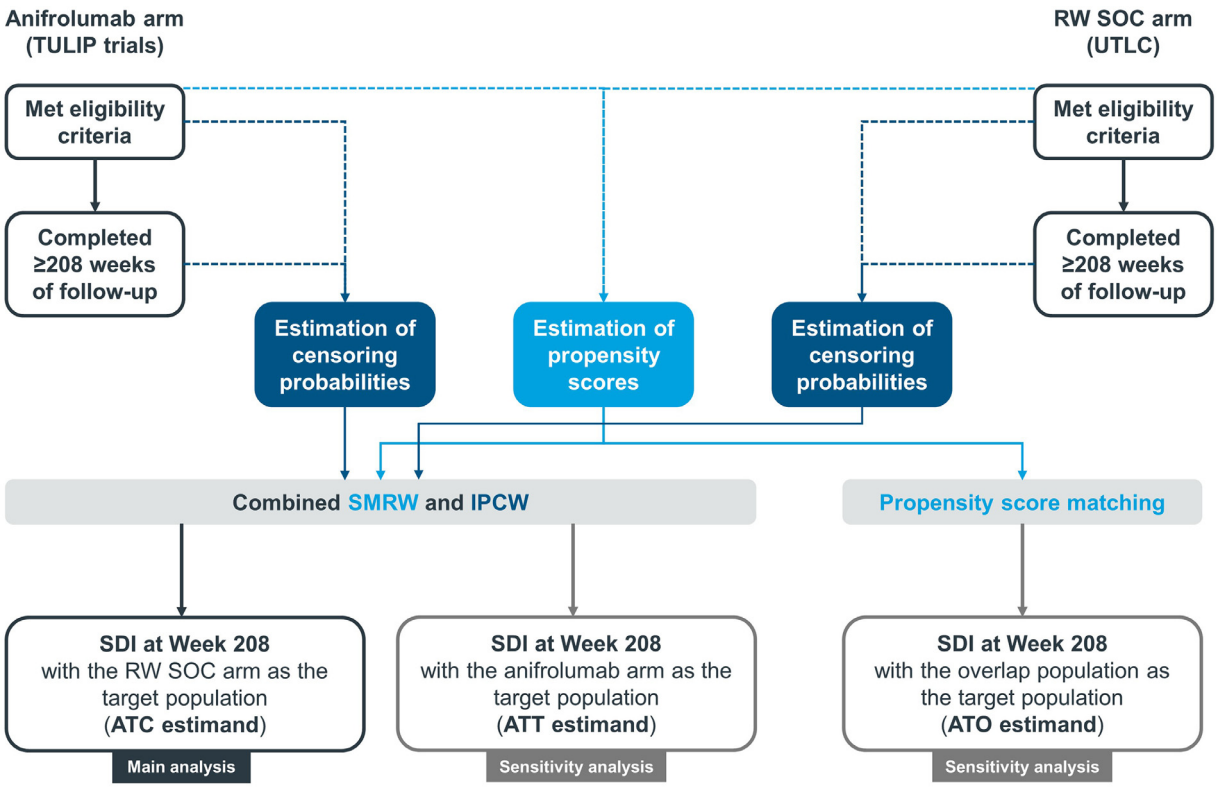

Figure 1. Diagram summarising methodology for primary study endpoint (SDI score at Week 208). ATC/ATO/ATT, average treatment effect in the control/overlap/treated population; IPCW, inverse probability of censoring weighting; RW, real-world; SOC, standard of care; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SMRW, standardised mortality ratio weighting; TULIP, Treatment of Uncontrolled Lupus via the Interferon Pathway; UTLC, University of Toronto Lupus Clinic.

replacement. For the ATO, patients in the anifrolumab arm with ≥208 weeks of follow-up were matched to patients in the RW SOC arm with ≥208 weeks of follow-up, and no IPCW was performed. Statistical analyses for the primary objective are summarised in Figure 1.

The average treatment effect on time to first SDI increase was estimated using a Cox regression model. Death, loss to follow-up, 208 weeks post-index, and end of study period were treated as censoring events. The estimated hazard rate in each treatment arm was reported along with the comparative hazard ratio (HR), with corresponding 95% CI and *P* value. The survival function for each treatment group was depicted using a weighted Kaplan-Meier plot, and median survival time with 95% CI was reported.

As sensitivity analyses, all primary analyses (ATC estimand) were repeated with an indexing period in the RW SOC arm restricted to January 1, 2005 to December 31, 2023. To better understand which components of SDI drove observed increases, a post hoc analysis was also conducted in patients with ≥208 weeks of follow-up to summarise organ damage accrual within each component between index and week 208. Methodological details are provided in Supplemental Materials. All analyses were conducted using R, version 4.1.2 [30].

Patient and public involvement

There was no patient or public involvement in this study.

RESULTS

354 patients from TULIP-1 and -2 were included in the anifrolumab arm, of whom 175 completed 208 weeks of follow-up. 561 patients from the UTLC were included in the RW SOC arm, of whom 345 completed 208 weeks of follow-up.

Baseline characteristics are presented in Table 1. Compared to patients in the anifrolumab arm, patients in the RW SOC arm were generally younger at SLE diagnosis (median age: 25 vs 31 years) and at index (median age: 31 vs 42 years), were less likely to be White (48.1% vs 64.7%), had lower disease activity at index (median SLEDAI-2K: 8 vs 10 points), and were more likely to have had proteinuria at index (39.6% vs 4.8%). SOC treatments received at index also differed, with patients in the RW SOC arm more likely to be receiving glucocorticoids (96.4% vs 81.4%), antimalarials (72.2% vs 67.5%), and immunosuppressants (61.9% vs 48.0%) than patients in the anifrolumab arm. Median baseline glucocorticoid dose was also higher in the RW SOC arm than in the anifrolumab arm (12.5 vs 10.0 mg/d). Gender, SDI, high BP or hypertension, and smoking history were similar between treatment arms.

The amount of missing baseline data was low across both treatment arms, with only race, BMI, high BP or hypertension, and smoking history having missing values. Visual inspection of missingness patterns and Little's test indicated that data were not missing completely at random ($P < .01$).

Following SMRW (ATC estimand), the 2 treatment arms were adequately balanced with respect to all baseline confounding variables except SLEDAI-2K score (SMD: −0.21) and proteinuria (SMD: −0.22) (Table 2). Adequate balance was also achieved for all confounding variables when targeting the ATT estimand (results in Supplemental Table S1).

Mean change in SDI from index to week 208 was 0.162 in the weighted anifrolumab arm and 0.587 in the weighted RW SOC arm (Table 3). After additionally adjusting for SLEDAI-2K score and proteinuria, the mean change in SDI from index to week 208 was 0.416 points lower (95% CI: −0.582, −0.249; $P < .001$) in the weighted anifrolumab arm than in the RW SOC arm (ATC). The sensitivity analysis that considered the ATT

Table 1
Baseline characteristics by treatment arm

Variable	Level	Anifrolumab arm (N = 354)		RW SOC arm (N = 561)	
		N	%	N	%
Year of diagnosis	pre-1970	0	0.00%	0	0.00%
	1970-1979	3	0.85%	6	1.07%
	1980-1989	17	4.80%	23	4.10%
	1990-1999	50	14.12%	181	32.26%
	2000-2009	117	33.05%	234	41.71%
	2010-2019	167	47.18%	117	20.86%
	2020-present	0	0.00%	0	0.00%
Age at diagnosis (y)	Mean (SD)	32.60 (11.95)		27.31 (12.04)	
	Median (Q1, Q3)	31.00 (23.00, 41.00)		25.00 (18.00, 35.00)	
Year of index	1995-1999	0	0.00%	46	8.20%
	2000-2004	0	0.00%	116	20.68%
	2005-2009	0	0.00%	129	22.99%
	2010-2014	0	0.00%	122	21.75%
	2015-2019	354	100%	126	22.46%
	2020-present	0	0.00%	22	3.92%
Age at index[a] (y)	Mean (SD)	42.57 (11.97)		34.09 (12.16)	
	Median (Q1, Q3)	42.00 (34.00, 50.00)		31.00 (24.00, 43.00)	
SLE duration at index (y)[a]	Mean (SD)	9.58 (8.59)		6.78 (6.46)	
	Median (Q1, Q3)	7.00 (3.00, 15.00)		4.77 (1.60, 9.54)	
Gender[a]	Male	27	7.63%	65	11.59%
	Female	327	92.37%	496	88.41%
Race[a]	White	229	64.69%	270	48.13%
	Black	46	12.99%	121	21.57%
	Native North American	4	1.13%	6	1.07%
	Other	67	18.93%	155	27.63%
	Missing	8	2.26%	9	1.60%
BMI at index	<18.5	8	2.26%	15	2.67%
	≥18.5 and <25	145	40.96%	148	26.38%
	≥25 and <30	77	21.75%	82	14.62%
	≥30 and <35	76	21.47%	44	7.84%
	≥35	48	13.56%	10	1.78%
	Missing	0	0.00%	262	46.70%
SLEDAI-2K score at index[a]	Mean (SD)	11.38 (3.82)		10.36 (4.90)	
	Median (Q1, Q3)	10.00 (8.00, 13.00)		8.00 (6.00, 12.00)	
SDI score at index[a]	0	241	68.08%	358	63.81%
	1	59	16.67%	118	21.03%
	≥2	54	15.25%	85	15.15%
Serum creatinine level at index (mg/dL)	<0.5	20	5.65%	21	3.74%
	≥0.5 and <1.2	323	91.24%	505	90.02%
	≥1.2 and ≤2	11	3.11%	35	6.24%
Proteinuria at index[a]	Yes	17	4.80%	222	39.57%
	No	337	95.20%	339	60.43%
Glucocorticoid use at index[a]	Yes	288	81.36%	541	96.43%
	No	66	18.64%	20	3.57%
Glucocorticoid dose at index (mg/d)[a]	Mean (SD)	8.98 (7.31)		14.66 (10.16)	
	Median (Q1, Q3)	10.00 (5.00, 10,00)		12.50 (7.50, 20.00)	
Antimalarial use at index[a]	Yes	239	67.51%	405	72.19%
	No	115	32.49%	156	27.81%
Immunosuppressant use at index[a]	Yes	170	48.02%	347	61.85%
	No	184	51.98%	214	38.15%
High BP or hypertension at index[a]	Yes	114	32.20%	167	29.77%
	No	225	63.56%	393	70.05%
	Missing	15	4.24%	1	0.18%
History of smoking at index[a]	Yes	79	22.32%	120	21.39%
	No	260	73.45%	430	76.65%
	Missing	15	4.24%	11	1.96%

BMI, body mass index; BP, blood pressure; Q1/Q3, first/third quartile; RW SOC, real-world standard of care; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.
[a] Denotes confounding variable.

(−0.337; 95% CI: −0.524, −0.150; $P < .001$) was consistent with ATC results. Propensity score matching in the subgroup of patients with ≥208 weeks of follow-up also favoured treatment with anifrolumab (−0.370; 95% CI: −0.578, −0.163; $P = .002$) (all results in Table 3).

In post hoc analyses, the largest increases in SDI were observed in the musculoskeletal, ocular, and renal systems (Supplemental Table S5 and Fig S2), with the largest single-component increases observed in avascular necrosis (41 and 0 points accrued in the RW SOC and anifrolumab arms, respectively), cataracts (28 and 7 points accrued, respectively), and end-stage renal disease (15 and 0 points accrued, respectively).

Patients in the anifrolumab arm were 59.9% less likely (HR: 0.401; 95% CI: 0.213, 0.753; $P = .005$) to experience an

Table 2
Baseline confounders pre- and post-SMRW (ATC estimand)

Variable	Level	Standardised mean difference	
		Pre-SMRW	Post-SMRW
Age at index	Mean	0.70	−0.09
Age at index, squared	Mean	0.69	−0.08
SLE duration at index	Mean	0.43	0.04
Gender	Male	−0.12	−0.13
Race	White	0.33	0.13
	Black	−0.20	0.01
	Native North American	<0.01	0.07
	Other	−0.19	−0.17
SLEDAI-2K score at index	6-10 points	−0.26	−0.21
SDI score at index	0	0.09	<0.01
	1	−0.11	−0.02
	≥2	<0.01	0.02
Proteinuria at index	Yes	−0.71	−0.22
Glucocorticoid use at index	Yes	−0.81	−0.02
Glucocorticoid dose at index	<5	0.38	−0.09
	≥5 and ≤7.5	0.12	−0.11
	>7.5 and ≤10	0.28	−0.04
	>10 and ≤20	−0.27	0.08
	>20 and ≤40	−0.37	0.12
Antimalarial use at index	Yes	−0.10	0.13
Immunosuppressant use at index	Yes	−0.28	−0.03
High BP or hypertension at index	Yes	0.08	−0.13
History of smoking at index	Yes	0.03	0.05

ATC, average treatment effect in the control population; BP, blood pressure; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SMRW, standardised mortality ratio weighting.
Note that the values in this table were obtained following imputation for missing variables.

increase in SDI score within 208 weeks than patients in the RW SOC arm (Fig 2). Early separation of the weighted Kaplan-Meier curves was observed, with an estimated 96% of patients in the anifrolumab arm (95% CI: 92%, 99%) not experiencing organ damage progression by week 52 compared to 89% of patients in the RW SOC arm (95% CI: 86%, 92%).

When the indexing period in the RW SOC arm was restricted to January 1, 2005 to December 31, 2023, 362 patients from the UTLC were included in the RW SOC arm. Results are presented in Supplemental Materials, including baseline characteristics (Supplemental Table S2) and covariate balance following SMRW (Supplemental Table S3). The mean change in SDI from index to week 208 was 0.270 points lower (95% CI: −0.429, −0.112; $P < .001$) in the weighted anifrolumab arm compared to the RW SOC arm (Supplemental Table S4). Patients in the anifrolumab arm were 41.0% less likely (HR: 0.590; 95% CI: 0.290, 1.200; $P = .138$) to experience an increase in SDI within 208 weeks than patients in the RW SOC arm (Supplemental Fig S1).

DISCUSSION

The accumulation of organ damage in patients with SLE is associated with numerous unfavourable outcomes, including multimorbidity, increased health care costs, and ultimately, increased mortality [31–35]. A recent systematic review and meta-analysis estimated that the standardised mortality ratio for patients with SLE was 2.87 times higher relative to the general population [36]. It has also been estimated that a 1-point increase in SDI is associated with a 34% increase in the relative rate of death [33]. These figures highlight the importance of controlling disease activity and reducing consumption of glucocorticoids for preventing organ damage, improving prognosis, and enhancing quality of life in patients with SLE, and are recommended strategies by the European Alliance of Associations for Rheumatology [2].

The connection between low disease activity and reduced organ damage accrual has been demonstrated in many studies [3,37–40]. Longer periods spent in Lupus Low Disease Activity State (LLDAS) or remission are associated with greater reductions in disease flare rates and organ damage accrual. Indeed, a recent study found that *any* duration of sustained LLDAS or remission >3 months was associated with reduced organ damage accrual, with increasingly longer periods of sustained LLDAS corresponding to increasingly protective associations [40]. Glucocorticoids—although a mainstay of SLE management—have also been linked to irreversible organ damage in this population [3–5,41,42].

Previous analyses of TULIP trial data have demonstrated the effectiveness of anifrolumab for controlling disease activity while simultaneously reducing glucocorticoids [14]. A post hoc analysis of TULIP-1 and -2 found that anifrolumab was

Table 3
Estimated difference between treatment arms in change in SDI score between index and 208 weeks post-index (all estimands)

Analysis	Methods			Anifrolumab arm		RW SOC arm		Estimated mean difference in change in SDI[b] (95% CI)	*P*
	Confounding adjustment	Informative censoring adjustment	Estimand	N	Mean change in SDI[a]	N	Mean change in SDI[a]		
Primary	SMRW	IPCW	ATC	354	0.162	561	0.587	−0.416 (−0.582, −0.249)	< .001
Sensitivity	SMRW	IPCW	ATT	354	0.224	561	0.561	−0.337 (−0.524, −0.150)	< .001
	Propensity score matching[c]	n/a	ATO	116	0.201	116	0.571	−0.370 (−0.578, −0.163)	.002

ATC/ATO/ATT, average treatment effect in the control/overlap/treated population; IPCW, inverse probability of censoring weighting; n/a, not applicable; RW SOC, real-world standard of care; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SMRW, standardised mortality ratio weighting.
[a] Estimated following weighting for confounding and/or informative censoring, as specified in methods.
[b] Estimated following weighting for confounding and/or informative censoring, as specified in methods, and direct adjustment for baseline variables which remained imbalanced.
[c] 1:1 nearest-neighbour matching with replacement.

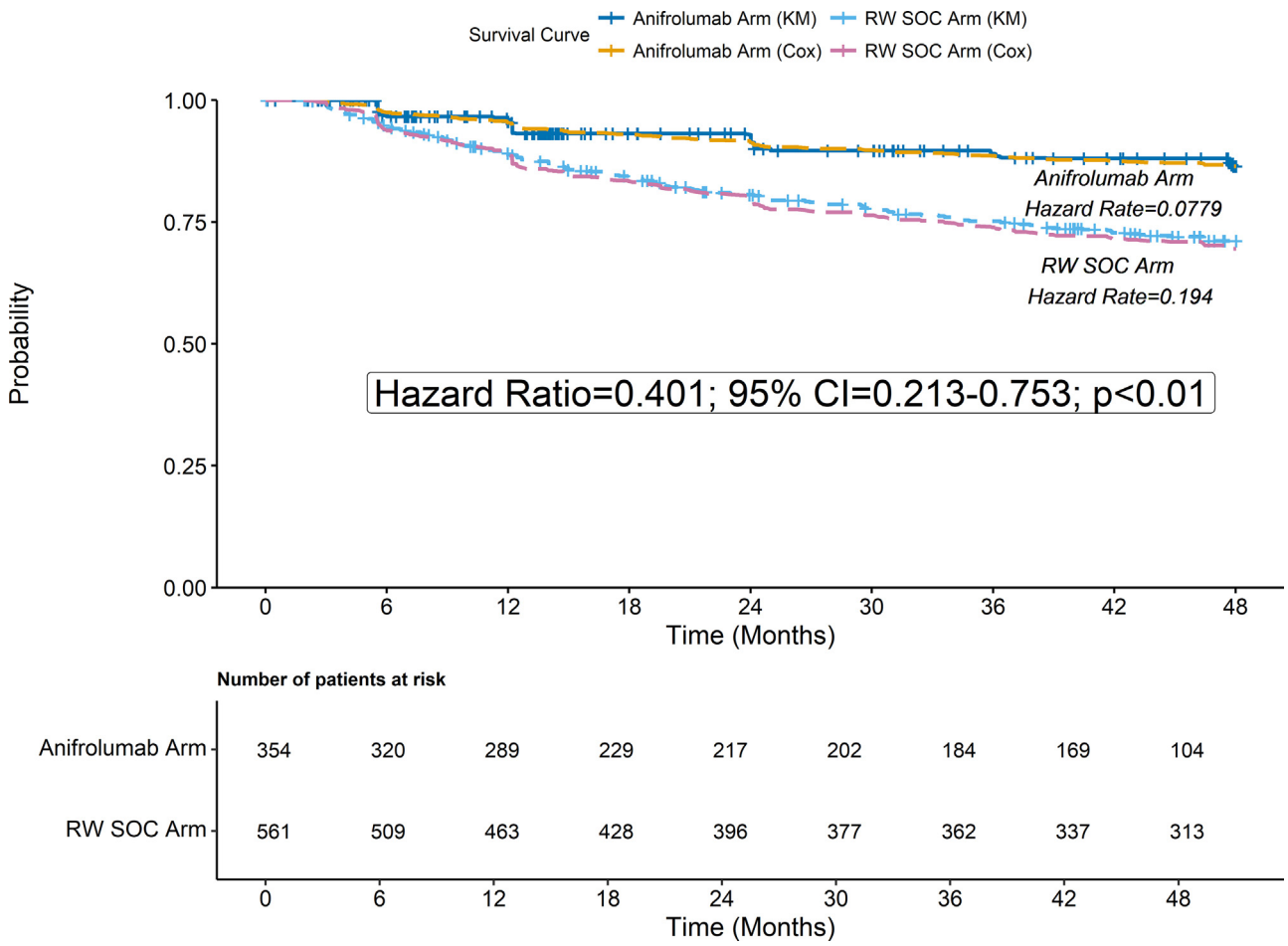

Figure 2. Kaplan-Meier curves for time to organ damage progression by treatment arm, with estimated hazard rates from fitted Cox models (ATC estimand). ATC, average treatment effect in the control population; KM, Kaplan-Meier; RW, real-world; SOC, standard of care.

associated with earlier attainment of LLDAS (HR: 1.76; 95% CI: 1.25, 2.30; $P < .001$), increased cumulative time in LLDAS (mean: 2.40 months vs 1.40 months, $P < .001$), and higher likelihood of sustained LLDAS ($P < .001$) than placebo [43]. Analyses of TULIP LTE data also found that 30.3% of patients treated with anifrolumab achieved disease remission by 4 years compared to 18.3% of patients in the placebo arm ($P = .06$) [18]. In TULIP-1 and -2, sustained glucocorticoid tapering was achieved by 51% of patients treated with anifrolumab plus SOC compared to 32% of patients treated with SOC alone ($P < .001$) [19]. However, no studies have previously demonstrated the effectiveness of anifrolumab for preventing long-term organ damage.

We used a RW external control arm to evaluate the effect of anifrolumab plus SOC in the TULIP-1 and -2 trials compared to RW SOC on long-term organ damage. After accounting for differences in baseline patient characteristics, including baseline SDI, our results suggest that anifrolumab plus SOC reduces organ damage accumulation in patients with moderately to severely active SLE. Over 4 years of follow-up, SDI increased by an average of 0.587 points in the RW SOC arm compared to 0.162 points in the anifrolumab arm, resulting in 0.416 fewer points of organ damage, on average, for patients who initiated 300 mg of anifrolumab in TULIP-1 and -2. Treatment with anifrolumab plus SOC was also associated with a 59.9% decreased risk of organ damage progression up to 4 years. Our results were consistent across 3 estimands (ie, ATT, ATC, and ATO), corresponding analytical methods (ie, propensity score weighting and matching), and inclusion period in the RW SOC arm, demonstrating robustness of study results.

The results of our study are also consistent with a previous external control arm study using the UTLC, which found that treatment with belimumab plus SOC was associated with a 0.424-point reduction in organ damage after 5 years (95% CI: −0.667, −0.201) and a 60.9% decreased risk of organ damage progression up to 5 years compared to RW SOC [22].

There are likely several mechanisms through which anifrolumab plus SOC reduces organ damage accumulation compared to RW SOC. The effects estimated in this study therefore represent a combination of causal pathways, including the direct effect of anifrolumab on controlling disease activity and its indirect effect on glucocorticoid reduction, as well as the effect of SOC restrictions imposed by the TULIP trial protocols (eg, no new antimalarials or immunosuppressants). Indeed, post hoc analyses revealed large increases in avascular necrosis and cataracts in the RW SOC arm during follow-up, both of which are linked to glucocorticoids [5]. Results should therefore be interpreted as estimates for the effect of the anifrolumab plus SOC *regimen* rather than the effect of anifrolumab alone.

Our study design and analysis were guided by the target trial emulation framework, which is increasingly used and recommended for external control studies as it provides a structured framework to help avoid common biases that typically affect analyses of RW data [44,45]. We applied key eligibility criteria from TULIP-1 and -2 to patients in the UTLC cohort to minimise selection bias, and we used propensity score weighting to minimise baseline confounding and retain a larger analytical sample than comparable matching methods. We also used censoring weighting to correct for loss to follow-up rather than conducting

a complete-case analysis, which is prone to survivorship bias due to patients who responded well to treatment being more likely to remain in the study. We used data from a high-quality RW cohort which has been used for numerous other studies in SLE [3,21,22,46,47]. Loss to follow-up from the UTLC has previously been shown to be low and not influence overall outcomes [46,48]; we also observed low amounts of missing data for the variables used in this study.

The estimated average treatment effect represents a clinically meaningful reduction in organ damage given the known rate of damage accrual in patients with SLE and the association of increased damage with poorer health-related quality of life and higher mortality [49]. A study of 2054 patients in the Hopkins' Lupus Cohort found that SDI increased at a rate of only 0.13 points per year [50], while a study of 4106 patients in the Asia-Pacific Lupus Collaboration cohort found that only 20% of patients with established disease developed new organ damage over a mean follow-up time of 2.6 years [51].

While key sources of bias were minimised through appropriate design and analysis, we acknowledge that the use of propensity score methods cannot replace a randomised trial, and our study has several limitations. Differential outcome misclassification could affect results due to the combination of trial and RW data sources. However, given that SDI changes slowly over time and patients in both treatment cohorts were expected to have a recording of SDI approximately once per year, significant bias is not expected. Changes in SOC over time could also affect study results, with the most notable change being the introduction of mycophenolate mofetil in the early 2000s and biologic agents since 2020 [2,52]. For this reason, we conducted sensitivity analyses in which we restricted the inclusion period for the RW SOC arm to January 1, 2005. We also excluded RW patients who received any biologic agents within 4 weeks prior to their index date but acknowledge that patients could have received them during follow-up. Finally, while the anifrolumab and RW SOC arms were balanced at baseline, balance was not guaranteed during follow-up. Our censoring models considered only baseline covariates, but loss to follow-up could also be influenced by post-baseline factors including disease activity.

We also acknowledge that more proactive attention to glucocorticoid sparing has been a feature of more recent SLE management guidelines [2], which may have influenced results. Indeed, glucocorticoid tapering in patients with a baseline dose of ≥10 mg/d was a feature of TULIP-1 and -2, although this only affected approximately 25% of patients. There have also been temporal improvements in the screening and management of key comorbidities, such as hypertension, hyperlipidaemia, and bone protection, such that we cannot completely exclude the possibility of residual confounding. Further analyses are planned to evaluate the effects of anifrolumab on daily and cumulative glucocorticoid dose.

CONCLUSION

Compared to an external control group, we observed clinically and statistically significantly lower organ damage accrual after 4 years in patients who initiated anifrolumab in the TULIP-1 and -2 trials, as well as a longer time to first organ damage progression. In addition to the proven effectiveness of anifrolumab for controlling disease activity, attaining LLDAS and remission, and enabling glucocorticoid tapering, this study shows that anifrolumab is effective for preventing long-term organ damage compared to RW SOC. The results of our study therefore support the benefit of adding anifrolumab to SOC for minimising long-term organ damage in patients with SLE.

Competing interests

ZT does not have any conflicts of interest to disclose. INB received research grants from AstraZeneca and Janssen; received consulting fees from AstraZeneca, GSK, Eli Lilly, Takeda, Dragonfly Therapeutics, and Janssen; and received speaker fees from AstraZeneca, GSK, and Janssen. RF received grants or contracts to his institution from AstraZeneca; received consulting fees, payment or honoraria, and support for attending meetings and/or travel from AstraZeneca; and participated in data safety monitoring or advisory boards for AstraZeneca. EM received research grants to his institution from AbbVie, Amgen, AstraZeneca, Biogen, BMS, EMD Serono, Eli Lilly, Janssen, GSK, Genentech, Novartis, Takeda, and UCB; received consulting fees from AbbVie, Alpine, AstraZeneca, Biogen, BMS, Dragonfly, EMD Serono, GSK, Gilead, Janssen, Novartis, Remegen, Roche, Takeda, and UCB; received honoraria from AstraZeneca, BMS, EMD Serono, and Roche; received support for attending meetings and/or travel from EMD Serono and Roche; has WO2022074123A1, WO2021184080A1, WO2023044530A1, WO2021094378A1, and WO2023057369A2 patents planned, issued or pending; participated in advisory boards for Dragonfly; held/holds the Board Director position in Rare Voices Australia and Exosome Biosciences; and owns stock or stock options of Dragonfly Therapeutics. RT is a former employee of and received stock or stock options from AstraZeneca. SC is an employee and owns stock or stock options of AstraZeneca. GA is an employee, owns stock or stock options of AstraZeneca; and has other financial interests from AstraZeneca. JK is an employee and owns stock or stock options of AstraZeneca. KA is an employee of IQVIA Ltd. HL is an employee of IQVIA Ltd. ER is an employee of IQVIA Ltd., which is contracted and funded by AstraZeneca to develop the content of the manuscript. AB is an employee and owns stock or stock options of AstraZeneca. DK is an employee and owns stock or stock options of AstraZeneca. MW is an employee and owns stock or stock options of AstraZeneca.

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Contributors

RT, SC, GA, JK, AB, DK, and MW were involved in study conceptualisation. ZT contributed to data acquisition. ZT, RT, SC, GA, JK, KA, HL, ER, and MW were involved in study design and methodology. KA, HL, and ER were involved in the analysis. KA, HL, and MW were involved in writing the original draft, and all authors were involved in reviewing and editing the manuscript. MW is responsible for the overall content as guarantor.

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Patient consent for publication

Patient consent was not required as this study involved secondary use of anonymised data.

Ethics approval

This study was approved by The University Health Network Research Ethics Board and Ontario Personal Health Information Protection Act [reference number 24-5028].

Provenance and peer review

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Data availability statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at: https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ard.2025.01.025.

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