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Adalimumab or etanercept as first line biologic therapy in enthesitis related arthritis (ERA) - a drug-survival single centre study spanning 10 years

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ABSTRACT

Objectives: To analyse and compare drug-survival of adalimumab and etanercept (and their biosimilars) in biologic-naïve patients with ERA (Enthesitis-Related Arthritis).
Methods: In this retrospective observational study, conventional statistics and machine-learning were applied to compare drug-survival (adalimumab, etanercept and their biosimilars initiated: 2009–2019) in ERA and identify determinants. **The primary outcome was discontinuation of treatment due to primary- or secondary-failure and adverse drug-reactions.**
Results: During the observation period, 99 of 188 patients with ERA on first-line TNF inhibitors (etanercept-*n*=108, adalimumab-*n*=80) discontinued their treatment (median survival-time 3.9years, 95%CI 2.6-4.9years). Adalimumab was associated with longer drug-survival compared to etanercept especially after an initial positive response, with the median time to treatment discontinuation 4.9years (95% CI 3.9–5.7) for adalimumab, compared to 2years (95%CI 1.4–4.0) for etanercept (HR of treatment-discontinuation-0.49, 95%CI 0.32–-0.75, *p*=0.001). Adjusted by propensity-score, adalimumab-methotrexate combination was associated with longer drug survival, compared to adalimumab-monotherapy (HR-0.41, 95%CI 0.20–0.85), etanercept-monotherapy (HR-0.28, 95%CI 0.15–0.53), and etanercept-methotrexate combination (HR-0.39, 95%CI 0.21–0.73). The presence of HLA-B27 was associated with longer drug-survival (HR-0.50, 95%CI 0.29–0.87) following an initial positive response. Higher-CRP at baseline was associated with higher rate of primary-failure (HR-1.68, 95%CI 1.08–2.62). Axial-ERA (sacroiliitis±spinal-involvement) was associated with poorer drug-survival for both primary- and secondary-failure (overall HR-2.03, 95%CI 1.22–3.40). Adjusted by propensity-score, shorter drug-survival was observed in patients with baseline-CRP≥12.15 mg/L, but only in the context of axial-ERA, not in peripheral-ERA (no sacroiliitis/spinal-involvement) (HR-2.28, 95%CI 1.13–-3.64).
Conclusion: Following an initial positive primary response, continuing methotrexate with adalimumab was associated with the longest drug-survival compared to adalimumab-monotherapy or etanercept-based regimens. Axial-ERA was associated with a poorer drug-survival. A CRP >12.15 in patients with axial-ERA was associated with a higher rate of primary-failure. Further prospective studies are required to confirm these findings.

Abbreviations

ADRs	Adverse drug reactions
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
CHAQ	Childhood health assessment questionnaire
CRP	C-reactive protein

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csDMARDs Conventional synthetic disease-modifying antirheumatic drugs
ERA Enthesitis-related arthritis
JADAS-CRP Juvenile arthritis disease activity score
HLA Human leukocyte antigen
IBD Inflammatory bowel disease
JIA Juvenile idiopathic arthritis
TNFi Tumour necrosis factor inhibitors
VAS Visual analogue score

Introduction

Enthesitis-related arthritis (ERA) is a sub-type of juvenile idiopathic arthritis (JIA) characterised by peripheral arthritis, enthesitis, and axial joint involvement. Compared to other JIA subtypes, ERA are more likely to have persistent disease activity into adulthood, and worse functional outcomes [1,2].

Over recent years, the widespread use of tumour necrosis factor inhibitors (TNFi) has revolutionised the treatment of ERA. Like other international guidelines [3], national guidelines in England advocated use of TNFi in ERA refractory to non-steroidal anti-inflammatories in 2015 [4]. This veered away from the prior guideline requiring the use of methotrexate prior to TNFi initiation which included no specific guidance for ERA separate to the other subtypes of JIA and did not include specific markers of axial disease [5]. Evidence of the long-term efficacy and sustainability of TNFi in ERA is limited by a paucity of data as previous studies were either focused on other JIA phenotypes or included only a small number of ERA patients [6–9].

Here we report a drug-survival analysis of first-line TNFi in our ERA-cohort. The primary objective of this study was to investigate drug-survival of adalimumab and etanercept and their biosimilars, with or without a combination of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). We also aimed to profile the major determinants influencing the retention of first-line TNFi in patients with ERA.

Methods

Patient population and outcome

A retrospective real-life observational study was conducted on biologic-naïve patients with ERA (fulfilling ILAR-criteria) [10], started on TNFi (etanercept or adalimumab, or its-biosimilar) at University College London Hospital (UCLH), from January 2009 to January 2019. We extracted data from our clinical database for adolescents and adults in January 2020.

Outcome

Patients are treated adhering to UK National Health System (NHS) regulations for the commissioning and funding of biologic treatments [4,11]. Response to therapy must be assessed and recorded every 3-6 months. The department uses ACR (American College of Rheumatology) pediatric response criteria [12]. Patients attaining at least ACR Pedi 30 response by the first 6 months were classified as having attained a positive primary response to treatment. Primary-failure was considered if the TNFi was discontinued due to a lack of primary response within the first 6 months, whereas secondary-failure was defined when treatment was withdrawn or switched due to the treatment failure (either due to the articular disease with new or worsening synovitis/enthesitis/worsening erosion, or ongoing/flare of uveitis or other extra-articular manifestations) [4] after attaining a positive primary response. **Patients who discontinued their treatment due to other reasons like – pregnancy, remission, lost follow-up, or moved away were right censored [13]in the survival analysis [14].**

The primary outcome was discontinuation of treatment, due to primary- or secondary-failure, and adverse drug-reactions (ADRs). A separate analysis was also performed on primary- and secondary-failure.

Table 1
Demographics and characteristics of the enthesitis-related arthritis patients at the beginning of 1st line TNFi

Characteristics	Overall, N = 188[1]	Etanercept, N = 108[1]	Adalimumab, N = 80[1]
Caucasian	120 (64%)	72 (67%)	48 (60%)
Male	141 (75%)	80 (74%)	61 (76%)
Age of onset, years	13.0 (3.1)	13.1 (3.0)	12.8 (3.2)
Missing - n (%)	*9 (5%)*	*1 (1%)*	*8 (10%)*
Age at TNFi initiation, years	16.2 (3.0)	16.3 (2.6)	15.9 (3.4)
Missing - n (%)	*24 (13%)*	*14 (13%)*	*10 (12%)*
Disease duration, months	37 (30)	38 (33)	36 (27)
Missing - n (%)	*24 (13%)*	*14 (13%)*	*10 (12%)*
CHAQ	1.7 (0.5)	1.8 (0.5)	1.6 (0.5)
Missing - n (%)	*43 (23%)*	*28 (26%)*	*15 (19%)*
Physician global VAS	64 (14)	66 (15)	61 (13)
Missing - n (%)	*62 (33%)*	*33 (31%)*	*29 (36%)*
Patient global VAS	68 (14)	70 (13)	66 (14)
Missing - n (%)	*46 (24.5%)*	*28 (26%)*	*18 (22.5%)*
Patient pain VAS	73 (12)	75 (12)	69 (13)
Missing - n (%)	*49 (26%)*	*31 (29%)*	*18 (22.5%)*
Swollen joint count	3.9 (2.0)	3.9 (2.0)	3.8 (2.1)
Missing - n (%)	*40 (21%)*	*23 (21%)*	*17 (21%)*
Tender joint count	5.3 (4.0)	5.2 (3.6)	5.5 (4.6)
Missing - n (%)	*92 (49%)*	*47 (43%)*	*45 (56%)*
Active joint count	3.4 (1.9)	3.5 (1.9)	3.3 (1.9)
Missing - n (%)	*63 (33%)*	*34 (31%)*	*29 (36%)*
Restricted joint count	2.6 (1.9)	2.7 (1.9)	2.6 (1.9)
Missing - n (%)	*73 (39%)*	*44 (41%)*	*29 (36%)*
BASDAI	6.3 (1.0)	6.2 (1.1)	6.4 (0.9)
Missing n (%)	*90 (48%)*	*53 (49%)*	*37 (46%)*
CRP[2], mg/L *(mean with SD)*	18 (24)	19 (30)	16 (14)
Median with IQR	12.8 (7-18.4)	12.9 (6.6-18.3)	12.2 (8-19.1)
Missing - n (%)	*29 (15%)*	*15 (14%)*	*14 (17.5%)*
JADAS27-CRP[3]	17.3 (3.5)	17.8 (2.9)	16.9 (4.0)
Missing - n (%)	63 (33%)	34 (31%)	29 (36%)
Axial-ERA	137 (73%)	80 (74%)	57 (71%)
Uveitis[4]	28 (15%)	8 (7%)	20 (25%)
Inflammatory bowel disease[4]	19 (11%)	13 (12%)	6 (8%)
HLA-B27 positive	134 (71%)	74 (69%)	60 (75%)
Methotrexate	121 (64%)	67 (62%)	54 (68%)
Sulfasalazine	38 (20%)	17 (16%)	21 (26%)
Observation period, months, *(mean with SD) Median with IQR*	32.6 (26.2) 24.8 (31.2)	30.3 (26.7) 20.2 (29.8)	35.7 (25.4) 31 (27.8)
Cause of discontinuation[5]			
Primary-failure	29 (15%)	20 (19%)	9 (11%)
Secondary-failure	59 (31%)	46 (43%)	13 (16%)
Adverse drug reactions	11 (6%)	4 (4%)	7 (9%)

[1] Statistics presented: n (number of events) (% of total patients); Mean (SD)n if not mentioned otherwise.
[2] CRP (C-reactive protein) normal value 0-5 mg/L.
[3] JADAS27CRP (Juvenile arthritis disease activity score – CRP) = physician global assessment (0-10-cm VAS) + patient global assessment (0-10-cm VAS) + Active joint count (0-27) + normalised CRP [(CRP-10)/10].
[4] Active disease or previous episodes during the observation period.
[5] n (number of events of the respective cause) (% of total events of discontinuation). BASDAI = Bath ankylosing spondylitis disease activity score, CHAQ = Childhood health assessment questionnaire, VAS = Visual analogue score.

Baseline data

The following data were collected at baseline (at TNFi initiation): demographics, age at onset, disease duration, baseline disease outcome-scores [CHAQ (childhood health assessment questionnaire), physician's global visual analogue score (VAS) i.e., physician's global assessment of the disease activity, patient's global VAS (patient's assessment on his/her general wellbeing), patient's pain VAS (overall pain score), tender

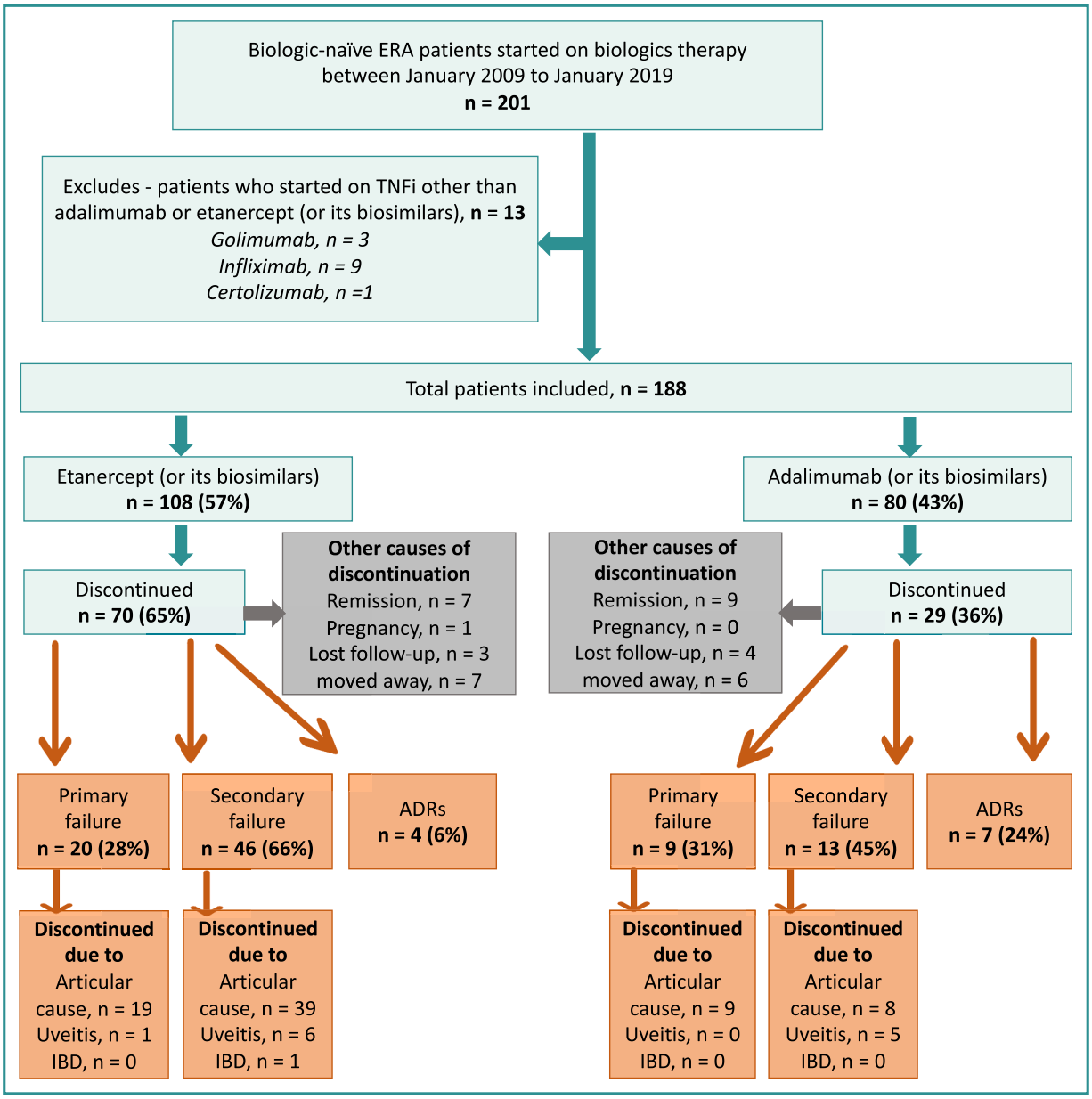

Fig. 1. Study population. Patients who discontinued due to remission, pregnancy, moved away, or lost in follow-up were right censored. ADRs = Adverse drug reactions, IBD = Inflammatory bowel disease, TNFi = Tumour necrosis factor inhibitor.

joint count (TJC), swollen joint count (SJC), active joint count (AJC), restricted joint count (RJC), JADAS-CRP (Juvenile arthritis disease activity score – CRP) [12], Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)], pre-TNFi inflammatory markers [C-reactive protein/CRP (normal-0-5mg/L)], and concomitant use of csDMARDs with corticosteroid. Uveitis & inflammatory bowel disease (IBD) (active disease or previous episodes), or new episodes during the observation period), axial-ERA (defined as presence of sacroiliitis/spinal-involvement on MRI/Magnetic resonance imaging) or peripheral-ERA (no sacroiliitis or spinal-involvement on MRI), and HLA-B27 were also recorded. Any given combination therapy of TNFi with methotrexate (or any other csDMARDs) were determined if they were already taking the csDMARDs and continued it following the TNFi initiation. Patients on combination therapy were right censored in the survival analysis if they discontinued the csDMARDs [15]. Similarly, monotherapy initiators were also right censored if csDMARD(s) were added later.

Statistical Analysis

All statistical analyses were performed using R (version 4.0.2, R Foundation for Statistical Computing, Vienna, Austria). Multiple imputation by Markov chain Monte Carlo equations under the missing-at-random assumption was used for handling missing values of covariates (exact numbers are shown in Table 1) at baseline. Forty imputed data sets were imputed, analysed, and pooled using Rubin's rules [16] by using *mice* [17] package in R.

Kaplan-Meier (K-M) analysis and propensity-score adjusted cox-regression were used to analyse time to treatment discontinuation. Propensity-score was estimated for each patient using logistic-regression adjusted for age at TNFi initiation, gender, race, disease duration, JADAS27-CRP (Juvenile arthritis disease activity score – CRP), concomitant treatment, axial disease, presence of uveitis (active disease or previous history), and IBD (active disease or previous history). To select covariates for the multivariable model we applied elastic-net [18] and partial least square regression (PLS) [10-fold cross-validation with

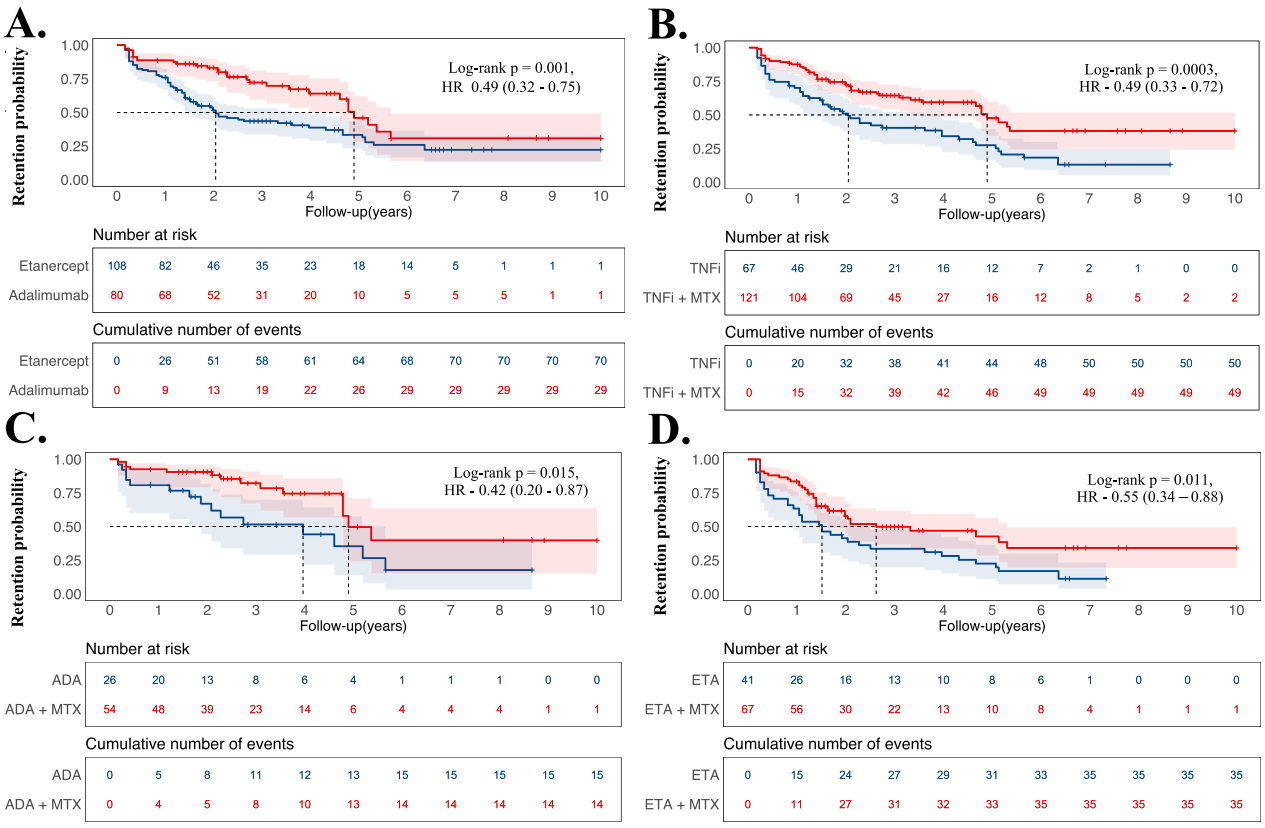

Fig. 2. (A-D): Kaplan-Meier (K-M) survival plots showing time to treatment-discontinuation by - (A) Adalimumab (ADA) versus Etanercept (ETA), **(B) tumour necrosis factor inhibitor (**TNFi)-monotherapy versus and TNFi-MTX **(methotrexate)** combination, **(C)** ADA-monotherapy versus and ADA-MTX combination, and **(D)** ETA-monotherapy versus and ETA-MTX combination. Dotted lines indicate median-survival time. Hazard ratio (HR) with 95% CI (confidence interval) of discontinuation of TNFi (unadjusted) are shown.

50-repetitions was applied to prevent model overfitting by using *plsRcox* [19]]. To check sensitivity of the findings, we adopted supervised machine-learning: survival-tree and random-forest (RF) survival. The survival-tree, using *rpart*[20] package, was constructed by growing the initial tree by binary-splitting and then pruning the tree to terminal-nodes with log-rank. Using maximally selected rank statistics with *ranger* package [21], RF for survival was adopted. Decision-trees were built using bootstrap dataset consisting of randomly selected samples from the original dataset with six randomly selected variables (mtry=6) for each decision-tree and minimum node size of 3 after model optimasation. 10,001 decision-trees were used allowing the output to be stabilised and to ensure the reliable predictive performance.

Ethical approval

This analysis was done as part of a service evaluation of clinical care. In accordance with National Health Service Research Ethics Committee guidelines, no formal ethical approval was required.

Results

A total of 188-patients were selected (Fig. 1) after excluding patients treated with TNFi other than adalimumab or etanercept (or its biosimilars), due to extremely low numbers. Of these 57% (108 of 188) started etanercept and 43% (80 of 188) adalimumab. 31% (59 of 188) patients discontinued TNFi due to secondary-failure and 15% (29 of 188) due to primary-failure. Mean age of onset of ERA was 13years (SD 3.1) (Table 1) and three quarters were male. Mean age of TNFi initiation was 16.2 (SD 3). About three-quarters had axial-disease and were HLA-B27 positive. 15% (n =28) of the patients had uveitis (details are illustrated in Supplementary Table 1) at baseline. Concomitant methotrexate was prescribed in 64% of the patients.

Adalimumab with methotrexate was shown to have the longest drug-survival

K-M analysis demonstrated longer drug-survival (Fig. 2A) of adalimumab, compared to etanercept (log-rank p=0.001) with median-time to treatment-discontinuation 4.9years (95%CI 3.9–5.7) and 2years (95%CI 1.4–4.0), respectively. Time-to treatment-discontinuation was significantly higher when TNFi was combined (Fig. 2B) with methotrexate (log-rank p=0.0003) compared to monotherapy. Combining methotrexate with adalimumab and etanercept was associated with significant prolongation of drug-survival compared to monotherapy (Fig. 2C-D) with hazard-ratio (HR) of 0.42 (95%CI 0.20–0.87, log-rank p=0.015) and 0.55 (95%CI 0.34–0.88, log-rank p=0.011), respectively.

After adjusting by propensity score, combination therapy of adalimumab with methotrexate was associated with better retention of treatment (Fig. 3) by reducing the risk by 59% (95%CI 15% to 80%, p=0.017), 72% (95%CI 47% to 85%, p=0.0008), and 61% (95%CI 27% to 79%, p=0.003) in comparison to adalimumab-monotherapy, etanercept-monotherapy, and etanercept-methotrexate combination, respectively.

Following the initial primary response, a longer drug-survival was observed in adalimumab treated patients compared to etanercept (log-rank test 0.0005) (Supplementary Figure 1A). Similar to the drug-survival of all causes, patients underwent secondary failure also showed shorter drug-survival if not being co-treated with methotrexate (Supplementary Figure 1B), but only in adalimumab-group (HR 0.27, 95%CI 0.09–0.85, log-rank p=0.015) (Supplementary Figure 1C), not in

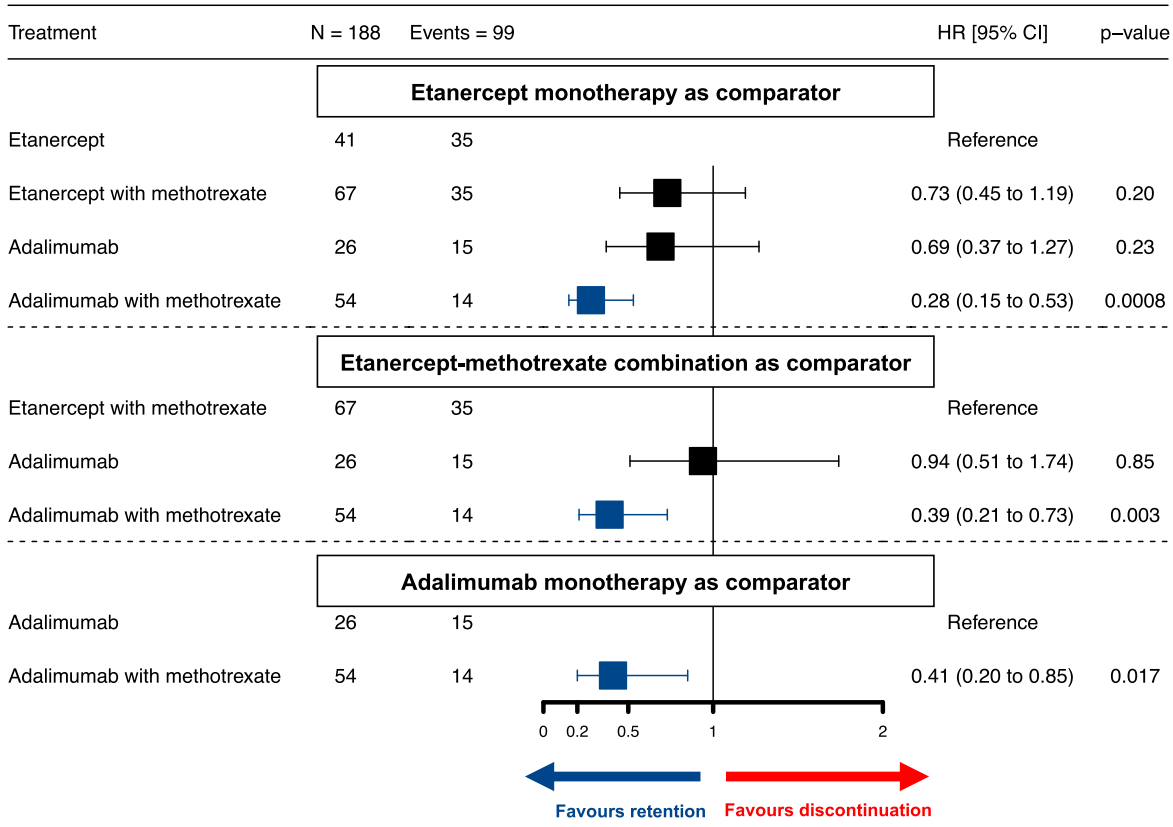

Fig. 3. Drug-survival comparing adalimumab and etanercept with or without methotrexate, adjusted by propensity-score†. Hazard ratio (HR) with 95% CI (confidence interval) of treatment-discontinuation. †*Propensity-score was estimated for each patient using logistic regression adjusted for age at TNFi initiation, gender, race, disease duration, JADAS27-CRP (Juvenile arthritis disease activity score – C-reactive protein/CRP), concomitant treatment, axial disease, and presence of uveitis or inflammatory bowel disease (active disease or previous history).*

etanercept treated patients (Supplementary Figure 1C). Propensity-score adjusted analysis confirmed these findings (Supplementary Figure 1E).

To explore if there was any difference between the cause of treatment discontinuation (either primary or secondary) i.e., worsening of articular disease versus uveitis, further comparison analysis was conducted stratified by the cause of discontinuation (Supplementary Figure 2). Favourable drug-survival of adalimumab was only demonstrated if worsening of joint disease led to the discontinuation (unadjusted HR 0.45, 95% CI 0.28-0.73, log-rank p<0.001) (Supplementary Figure 2A) and not for uveitis (Supplementary Figure 2B).

Other determinants of drug-survival

Concomitant methotrexate, CRP (log transformed), HLA-B27 positivity were associated with better drug-survival in the univariable analysis (Supplementary Table 2).

Covariates selected by PLS (Fig. 4A), and elastic-net regression were the same. In the multivariate regression (Fig. 4B), use of adalimumab (HR-0.49, 95%CI 0.31-0.875, p=0.0011), methotrexate (HR-0.47, 95% CI 0.32–0.71, p=0.0002) and HLA-B27 positivity (HR-0.58, 95%CI 0.38–0.88, p=0.01) were associated with longer drug-survival. Axial-ERA (HR-2.03, 95%CI 1.22–3.40, p=0.0067) and higher (log of) baseline-CRP (HR-1.29, 95%CI 1.04–1.60, p=0.023) associated with increased risk of drug-discontinuation. A sensitivity analysis (complete case) confirmed these findings (Supplementary Figure 3).

In our RF survival model (Fig. 4C), methotrexate and adalimumab were the two most influential factors (by Mean Decrease Gini where higher value means higher importance) to predict TNFi-survival. In survival-tree model (Fig. 4D) final nodes were split by concomitant-methotrexate, HLA-B27, TNFi baseline-CRP [splitting was based to minimise the Gini impurity; 12.15 was chosen by the rpart function [20]], and axial-ERA. K-M curve (Fig. 4D) showed poorer drug-survival of the axial-ERA patients with baseline-CRP≥12.15mg/L (node-11), compared to peripheral-ERA (node-9) irrespective of baseline CRP level (node-8). After propensity-score adjustment, axial-ERA patients with baseline-CRP≥12.1mg/L had higher rates of treatment-discontinuation (Fig. 4E), compared to peripheral-ERA patients with baseline-CRP≥12.15mg/L (HR-2.28, 95%CI 1.13-3.64, p=0.022) or patients with baseline-CRP<12.15mg/L irrespective of axial- or peripheral-disease (HR-1.98, 95%CI 1.30-3.03, p=0.0016).

In the subgroup of patients underwent secondary-failure, adalimumab, methotrexate, HLA-B27, and axial-ERA but not baseline-CRP, were associated with longer drug-survival (Supplementary Figure 4A-C). Whereas in the context of primary-failure, raised baseline-CRP and axial-disease were associated with unfavourable initial response to TNFi (Supplementary Figure 5A-C) while patients with concomitant methotrexate was more likely to show the initial response to TNFi (HR-0.43, 95%CI 0.20-0.93, p=0.032). The primary-response was not influenced by HLA-B27 or adalimumab.

Discontinuation due to ADRs

No difference was noted between etanercept and adalimumab if they were discontinued due to ADRs (Supplementary Figure 6). Infections and drug-induced liver injury were enlisted among the causes of treatment discontinuation secondary to ADRs are (Supplementary Table 3).

Discussion

This is one of the largest real-world studies examining the long-term

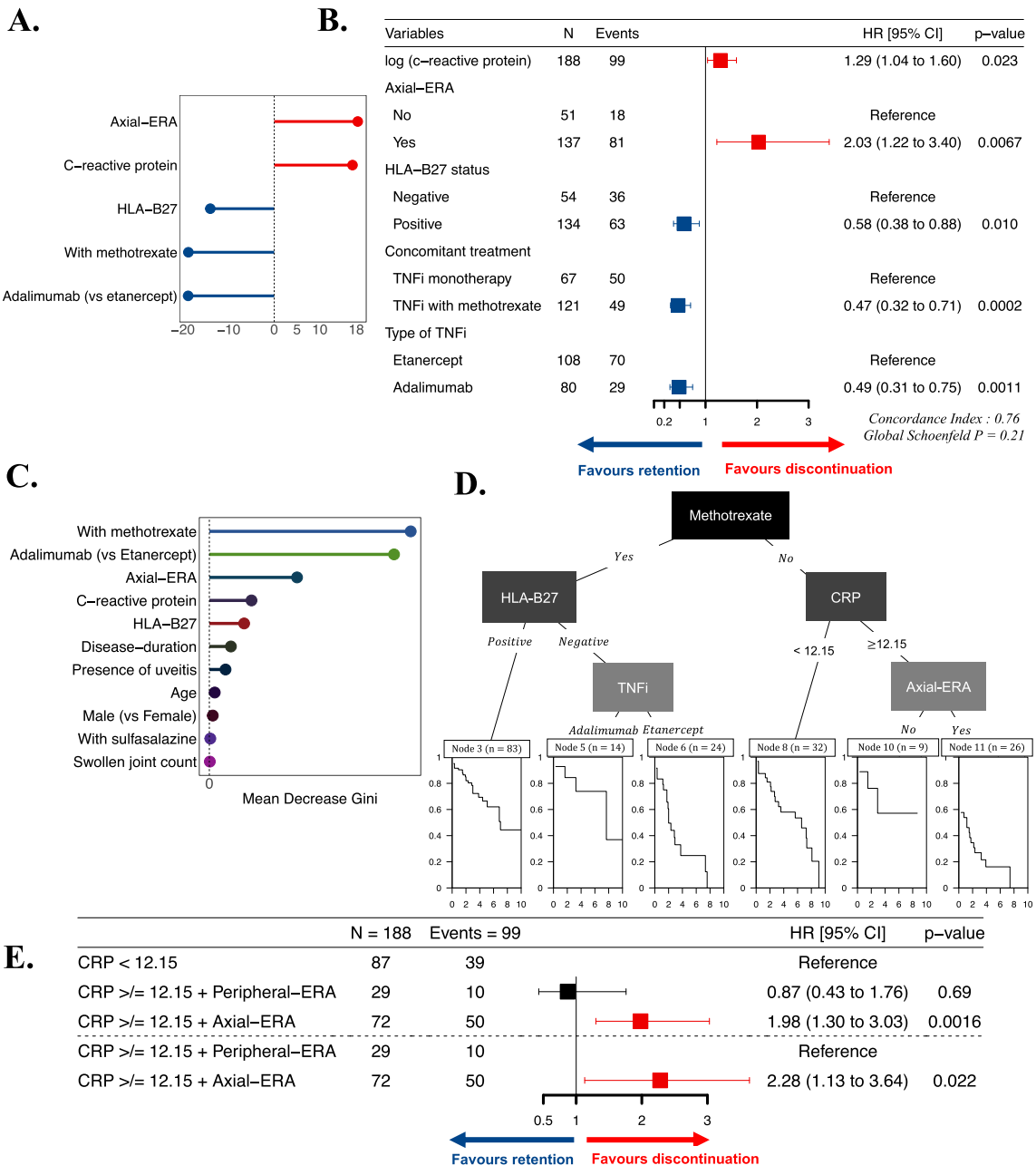

Fig. 4. A-E: Covariates predicting 10-year drug-survival of first-line tumour necrosis factor inhibitor (TNFi) in Enthesitis-related arthritis (ERA). A. Partial least squares regression model – covariates (ranked) with left-oriented bars favour TNFi-retention, whereas right-oriented bars favour discontinuation of TNFi. **B. Multivariable cox-regression (with multiple imputation)** – Hazard ratio (HR) with 95 % confidence interval (CI) of the risk factors for discontinuation of first-line TNFi **C. Random Forest model** – to predict the discontinuation of TNFi (error rate was 19.2%). Covariates (ranked) contributing to the random forest model are shown. **D. Survival tree** – terminal nodes to predict discontinuation of TNFi with Kaplan-Meier curves of each node. **E. Propensity-score† adjusted cox-regression** - interaction between CRP = C-reactive protein (normal 0-5 mg/L) and axial-ERA. †*Propensity-score was estimated for each patient using logistic regression adjusted for age at TNFi initiation, gender, race, disease duration, JADAS27-CRP (Juvenile arthritis disease activity score – CRP), concomitant treatment, axial disease, and presence of uveitis or inflammatory bowel disease (active disease or previous history).*

drug-survival of TNFi in biologic-naïve patients with ERA. Our patient cohort spans the adolescent and young adult age range representing a cohort in a unique developmental phase of life, biologically and psychosocially. The median TNFi-survival time of our patients was 3.9years which is consistent with other studies [6,7]. Our results show longer drug-survival being associated with adalimumab which was augmented by concomitant methotrexate and HLA-B27 positivity. A higher CRP as baseline was associated with a reduced primary response, whereas axial-disease was associated with increased primary- and secondary-failure.

A longer drug-survival associated with adalimumab compared to etanercept in ERA has never been shown before. Previous evidence suggests that combining methotrexate with adalimumab may reduce the development of anti-drug antibodies and a consequent loss of efficacy [22]. Adalimumab is more immunogenic than etanercept, and previous studies revealed more frequent detection of anti-drug antibodies to adalimumab compared to etanercept [23] leading to treatment failure or hypersensitivity. This is in keeping with our finding of longer drug-survival being associated with combination methotrexate and adalimumab. We found HLA-B27 positive status associated with longer

TNFi-survival for secondary-failure. This has not been described in ERA but has been shown in ankylosing spondylitis (AS) [24]. In contrast to our findings, elevated-CRP was shown be associated with better TNFi response in AS [25]. A previous study showed TNFi benefit in treating sacroiliac joint inflammation [26], however our finding of poorer drug-survival of TNFi in axial-ERA (with raised CRP) has not been previously described and requires further study.

We acknowledge this was a retrospective study with all the inherent weaknesses of such a methodology. Another limitation of our study is being single-centred. We were unable to assess the effect of intravenous, intra-articular or intramuscular steroid or concomitant NSAIDs due to incomplete records. Incomplete dosing record of methotrexate at multiple time-points precluded using dosing as an adjustment factor. Adherence to both methotrexate and TNFi may be a key determinant factor that is difficult to measure. This is especially pertinent in this age group who may have lower levels of adherence and more side effects with methotrexate [27]. Investigating the role of anti-drug antibodies on TNFi survival is an area for future study especially as this becomes part of standard clinical practice.

The longer drug-survival associated with adalimumab would need to be confirmed by a clinical trial comparing adalimumab and etanercept. Specific relationships that need further study include concomitant methotrexate including dosing, HLA-B27, CRP, and axial- versus peripheral-disease. This may inform future treatment strategies for ERA.

Contributors

MS, NH, AVM, and AB were involved in data collection. MS performed the analysis, RM and CD helped in the statistical analysis. MS, CF, ML, CC, and DS were involved in the design of the study design and data interpretation. All authors contributed and reviewed the manuscript's content before submission.

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Disclosure: None.

Patient consent for publication: not required.

Ethical approval: No ethical approval is required for retrospective clinical database analysis under National Health Service Research Ethics Committee.

Conflict of Interest

None.

Data availability statement

: Anonymised individual patient data will be shared upon reasonable request for research purposes.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2022.152038.

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