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ORIGINAL RESEARCH

First-time adverse drug reactions, survival analysis, and the share of adverse drug reactions in treatment discontinuation in real-world rheumatoid arthritis patients: a comparison of first-time treatment with adalimumab and etanercept

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ABSTRACT

Background: This study aims to compare nature and frequency of adverse drug reactions (ADRs), time to first ADR, drug survival, and the share of ADRs in treatment discontinuation of first-time treatment with adalimumab (ADA) and etanercept (ETN) in real-world RA patients.

Research design and methods: Retrospective, single-center cohort study including naïve patients treated between January 2003-April 2020. Time to first ADR and drug survival of first-time treatment were studied using Kaplan–Meier and Cox-regression models up to 10 years, with 2- and 5-year post-hoc sensitivity analysis. Nature and frequencies of first-time ADRs and causes of treatment discontinuation were assessed.

Results: In total, 416 patients (ADA: 255, ETN: 161, 4865 patient years) were included, of which 92 (22.1%) experienced ADR(s) (ADA: 59, 23.1%; ETN: 33, 20.4%). Adjusted for age, gender and concomitant conventional DMARD use, ADA was more likely to be discontinued than ETN up to 2-, 5- and 10-year follow-up (adjusted HRs 1.63; 1.62; 1.59 (all p<0.001)). ADRs were the second reason of treatment discontinuation (ADA 20.7%, ETN 21.4%).

Conclusions: Despite seemingly different nature and frequencies, ADRs are the second reason of treatment discontinuation for both bDMARDs. Furthermore, 2-, 5-, and 10-year drug survival is longer for ETN compared to ADA.

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Rheumatoid arthritis; adverse drug reactions; bDMARDs; biologicals; drug survival; real-world data

1. Introduction

Current cornerstone drug treatment of rheumatoid arthritis (RA) consists of various disease-modifying antirheumatic drugs (DMARDs). Biological DMARDs (bDMARDs) are prescribed in patients with poor prognostic factors and/or insufficient response on conventional synthetic DMARDs (csDMARDs) [1]. Two of the most frequently prescribed bDMARDs are adalimumab (ADA) and etanercept (ETN). After starting bDMARD treatment, patients may experience various adverse drug reactions (ADRs), which may lead to reduced drug adherence and cause high burden [2,3]. ADRs are a cause of dose adjustment or, if the burden is too high, discontinuation of and switching to another treatment [2,4,5]. Hence, ADRs caused by DMARDs have been of scientific interest for years [6,7]. Thus far, little is known about time to first ADR, and the share of ADRs in causes of first-time treatment discontinuation of different bDMARDs in daily practice.

Despite the differences in characteristics of the biologicals, it is assumed from indirect comparison of clinical trial data that ADA and ETN have comparable efficacy and safety profiles, and they are therefore generally seen as interchangeable [8–10]. However, several observational studies on ADA and ETN drug survival do show differences between these drugs [11–13]. So far, little is known about first-time drug survival. As far as we know, there have been no previous studies comparing time to first ADR and drug survival of first-time drug use for bDMARDs in RA.

Since 2003, several hospitals in the Netherlands have been working together in the Dutch Rheumatoid Arthritis Monitoring (DREAM-RA) registry. This registry contains information on patients that is collected during regular visits to their rheumatology department, including their diagnosis, disease course and outcomes, and on drug treatment and ADRs. The data from the registry can be used to improve quality and efficiency of RA health care by sharing knowledge and experiences [14]. Several studies have been performed since the start of the registry [15–17]. However, data from the DREAM-RA registry has not yet been used to examine and to compare time to first ADR, nature of ADRs, share of ADRs as reason for

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treatment discontinuation and drug survival in patients using ADA and ETN.

In this study, we aim to compare frequencies and nature of ADRs, survival to first ADR and drug survival in real-world patients using ADA and ETN for the first time. Furthermore, we aim to compare the share of ADRs in causes of first-time treatment discontinuation.

2. Methods

2.1. Study design

In this single-center retrospective observational cohort study, we assessed the time to first ADR and drug survival of first-time treatment in patients using ADA or ETN. Furthermore, frequencies of first-time ADRs (exposure adjusted incidence rate, EAIR) as well as the nature of first-time ADRs were assessed for ADA and ETN. The share of ADRs as cause of discontinuation of therapy was calculated. RA patients from Medisch Spectrum Twente (MST) hospital, Enschede, the Netherlands, participating in the DREAM-RA registry between January 2003 and April 2020 were eligible for inclusion. MST is a large teaching hospital, in the east of the Netherlands. MST DREAM-RA patients comprise the largest and most systematically monitored group within the DREAM-RA registry.

2.2. Data source

In 2003, the DREAM-RA registry started monitoring bDMARD use of RA patients [14]. In the registry, both patients and rheumatology healthcare professionals (HCPs) report information on treatments, outcomes and ADRs using the web-based mijnreumacentrum.nl application [18]. Patient reported ADRs have to be verified by a rheumatology HCPs before definite inclusion in the registry database. Since December 2015, the DREAM-RA registry and Netherlands Pharmacovigilance Center Lareb (Lareb) cooperate on ADR registration [14]. Since then, all verified ADRs registered at mijnreumacentrum.nl are directly forwarded anonymously to Lareb and evaluated and classified by trained scientific assessors. Furthermore, all ADRs that were prospectively collected between 2003 and December 2015 were retrospectively forwarded to Lareb. Before inclusion in the DREAM-RA registry, all patients gave written informed consent. Since data were collected in daily clinical practice, no further ethical approval was required according to Dutch law.

2.3. Inclusion of patients and assessment of treatment

For the assessment of treatment, all adult RA patients that started DMARDs between 1 January 2003 and 30 April 2020 were eligible. Patients had to be bDMARDs naïve, which meant patients had not previously been prescribed any bDMARD treatment (including other tumor necrosis factor alpha (TNF-α) inhibitors (ATC code L04AB), interleukine-6 inhibitors (ATC code L04AC) or CD20 monoclonal antibodies (ATC code L01FA), for any period of time. In accordance with Dutch biologic treatment guidelines and DREAM-RA treatment protocols, all patients received at least one csDMARD prior to bDMARD use. Prior or concomitant use of csDMARDs during bDMARD therapy was no exclusion criterium.

For both ADA and ETN, only treatment periods of at least 15 days were included. In general, patients received 40 mg ADA biweekly or 50 mg ETN weekly, via subcutaneous injection. In case of low disease activity, dosage frequency could be decreased at the discretion of the treating rheumatologist. End of drug treatment was defined as a treatment discontinuation, characterized by absence of prescription of either ADA or ETN in the DREAM-RA registry, for at least 90 days. Concomitant csDMARDs use was defined as use of hydroxychloroquine (HCQ), methotrexate (MTX), sulfasalazine (SSZ) and/or leflunomide (LEF) for at least 15 consecutive days during bDMARD treatment. This 15-day requirement is in accordance with the Dutch health care system, in which patients usually receive a first-time prescription for 14 days.

2.4. Assessing adverse drug reactions

2.4.1. Frequency and nature of first-time ADRs

In this study, an ADR was considered first-time ADR if attributed to either ADA or ETN and closest to start date of the first bDMARD treatment of the patient. Nature of ADRs were coded by trained assessors from Lareb in Preferred Terms (PTs) and System Organ Classes (SOCs) using the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA is an international standardized medical terminology, developed by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) [19]. Since patients could have more than one ADR on the date of experiencing their first ADR, the number of ADRs could exceed the number of patients experiencing an ADR.

ADRs were designated serious or non-serious according to the Council for International Organizations of Medical Sciences (CIOMS) criteria for seriousness of ADRs. For an ADR to be designated serious, the following had to apply to the ADR on patient level: (1) results in death, (2) is life-threatening, (3) requires inpatient hospitalization or prolongation of existing hospitalization, (4) results in persistent or significant disability/incapacity or (5) is a congenital anomaly/birth defect [20].

2.4.2. Share of adverse drug reactions in causes of treatment discontinuation

Causes of treatment discontinuation were assessed to determine the share of ADRs as reason for treatment discontinuation in the total number of patients discontinuing treatment. In DREAM-RA, practitioners can select multiple reasons for stopping a treatment. These categories are: 'Ineffectiveness,' 'ADRs,' 'Ineffectiveness and ADRs,' 'Sufficient effect,' 'Lost to follow-up,' 'Death,' 'Trial instructions,' 'End of trial,' 'Low disease activity/remission,' and 'Other.' If the category 'Other' is selected, practitioners can optionally fill in a description of the stop reason in an open-ended text field. If available, the description in the text field was categorized when fitting into an already existing category. If no category was applicable, it was categorized as 'Other.'

2.5. Data analysis

Time to first ADR was assessed by calculating time between start date of treatment with ADA or ETN and the date of first ADR in years. Survival of first-time treatment was assessed by calculating time between start date of treatment with ADA or ETN and date of discontinuation of ADA or ETN in years. Patients were followed up to 10 years. To obtain insight into shorter-term survival, a post-hoc sensitivity analysis with follow-up data up to 2 and 5 years was performed. For both time to first ADR and drug survival, patients still being treated past 30 April 2020, were censored at this date. Patients that died during their first-time treatment were censored at date of death. Switching of ADA to ETN or vice versa was not taken into consideration but considered as stop of treatment with the particular drug.

The frequencies of ADRs were calculated as Exposure Adjusted Incidence Rate (EAIR). The EAIR is expressed as ADRs per patient year and calculated per treatment using equation 1:

$$\textit{Exposure Adjusted Incidence Rate} = \frac{\textit{Total number of first time ADRs during first time drug use}}{\textit{Total time at risk of experiencing an ADR during first time drug use}} \quad (1)$$

The nature of ADRs was categorized according to MedDRA SOC categories. The number of serious ADRs was counted per SOC per treatment. The frequency of types of ADRs experienced as first-time ADR is expressed in percentages and calculated per SOC per treatment using equation 2:

$$\textit{Frequency of type o fADRs} = \frac{\textit{Number of ADRs belonging to specific SOC pertreatment}}{\textit{Total number of ADRs per treatment}} x100\% \quad (2)$$

To assess the share of ADRs as a proportion of the total number of treatment discontinuations, the causes leading to treatment discontinuation were counted per category and summed. Frequencies were calculated per treatment and expressed in percentages, using equation 3:

$$\textit{Frequency of category of stop reasons} = \frac{\textit{Number of patients in specific category of stop reasons per treatment}}{\textit{Total number of patients discontinuing treatment per treatment}} x100\% \quad (3)$$

2.6. Statistical analysis

Both time to first ADR during first-time treatment and drug survival of first-time treatment were first studied by Kaplan–Meier analysis survival curves for up to 10 years of follow-up. Next, differences in survival time between bDMARDs were statistically tested with Cox proportional hazard models and expressed as hazard ratio's (HRs). Both crude and adjusted analyses controlling for potential confounders were performed, including age at start of the treatment, gender and concomitant csDMARD use. Compliance with the proportional hazards assumption was checked by generation a time-dependent covariate and testing the interaction term with the predictor(s) of the model in an extended Cox regression model [21]. A nonsignificant chi-square test for the total change in model fit by addition of the interaction term(s) was considered indicative of compliance with the assumption. Concomitant csDMARD use was defined as continuous use of MTX, HCQ, SSZ, and/or LEF for more than 14 days. Post-hoc sensitivity analysis of survival up to 2 and 5 years were also performed.

All statistical analysis were performed in IBM SPSS Statistics (version 26). Survival curves were created in R (version 4.0.3) [22]. A p-value of less than 0.05 was regarded as statistically significant.

3. Results

Of the 1,115 MST DREAM-RA patients that participated in the DREAM-RA registry during the selected period, 416 (37.3%) were prescribed ADA or ETN as a first-time bDMARD treatment and were included in this study, with a total follow-up time of 4865 patient years. Figure 1 shows the flowchart of patient selection. Characteristics of the study population are provided in Table 1.

Of the 416 patients that were included in this study, a total of 255 patients (61.3%) used ADA and 161 (38.7%) used ETN. A total of 328 patients (78.8%) concomitantly used csDMARDs. Of the 255 ADA using patients, 211 patients (82.7%) concomitantly used one or more csDMARD(s). A total of 140 patients (66.4%) used only MTX, 40 patients (19.0%) MTX and another csDMARD and 31 patients (14.7%) did not use MTX in combination with ADA. Of the 161 ETN using patients, 117 patients (72.7%) concomitantly used one or more csDMARD(s). A total of 70 patients (51.3%) only used MTX, 28 (23.9%) used MTX and another csDMARDs and 19 patients (16.2%) did not use MTX in combination with ETN. For both ADA and ETN using patients with concomitant use of csDMARDs, patients that did not use MTX concomitantly, used HCQ, SSZ and/or LEF alone or in several combinations.

3.1. Frequency and nature of adverse drug reactions

The EAIRs for ADA and ETN were 0.12 and 0.07, respectively, for patients experiencing a first-time ADR per patient years at risk.

A total of 112 first-time ADRs attributed to therapy with either ADA or ETN were assessed. Table 2 gives and overview of the nature of ADRs per SOC, according to MedDRA terminology, and shows that the most frequently reported first-time ADRs attributed to ADA were in the SOC 'Skin and subcutaneous tissue disorders (18, 24.7%, including pruritus), followed by 'Infections and infestations (12, 16.4%, including tract infections) and 'General disorders and administration site conditions (7, 9.6%). For ETN, these were 'Infections and Infestations' (20.5%, such as pneumonia), 'General disorders and administration site conditions' (15.4%, such as fatigue and swelling), and 'Respiratory, thoracic, and mediastinal disorders (15.4%,

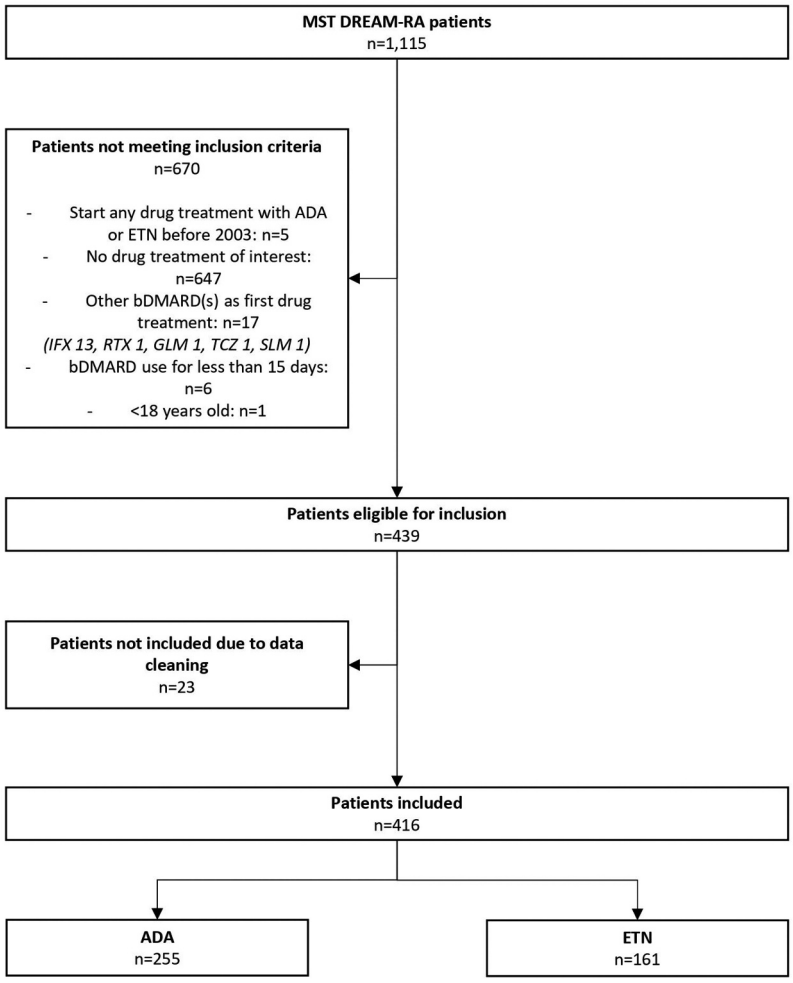

Figure 1. Flowchart of selection of DREAM-RA patients on first-time treatment with adalimumab or etanercept from the MST hospital. Of the 1,115 DREAM-RA patients from the MST hospital, a total of 416 patients were included: 255 for ADA treatment, 161 for ETN treatment. ADA: adalimumab, bDMARDs: biological disease modifying antirheumatic drugs, DREAM-RA: DutchDutch Rheumatoid Arthritis Monitoring registry, ETN: etanercept, GLM: golimumab, IFX: infliximab, MST: Medisch Spectrum Twente, Enschede, the Netherlands, RA: rheumatoid arthritis, RTX: rituximab, SLM: sarilumab, TCZ: tocilizumab.

Table 1. Characteristics of included DREAM-RA patients selected on first-time treatment with adalimumab or etanercept from the MST hospital, overall and stratified per treatment.

Characteristics	Overall	Adalimumab	Etanercept
Total, N (% of patients in group)	416	255 (61.3)	161 (38.7)
Age at start, years (±SD)	55.3 (±12.8)	54.5 (±13.1)	56.7 (±12.3)
Female gender, N (%)	289 (69.5)	182 (71.4)	107 (66.5)
ACPA positivity, N (%, missing %)	248 (59.6, 22.8)	150 (58.8, 20.0)	98 (60.1, 26.7)
RF positivity, N (%, missing %)	295 (70.9, 18.0)	175 (68.6, 17.3)	120 (74.5, 19.3)
Patients with ADR(s), N (%)	92 (22.1)	59 (23.1)	33 (20.5)
Patients concomitantly using csDMARDs (%)	328 (78.8)	211 (82.7)	117 (72.2)
DAS-28 patients with ADR(s) (±SD, missing %)	4.19 (± 1.64, 13.0)	4.12 (± 1.70, 13.6)	4.68 (± 1.52, 38.3)
DAS-28 patients without ADR (±SD, missing %)	4.32 (± 1.46, 10.5)	4.10 (± 1.38, 10.1)	4.33 (± 1.52, 12.1)
DAS-28 at time of first ADR (±SD, missing %)	3.04 (± 1.49, 13.0)	2.94 (± 1.54, 10.2)	3.24 (± 1.37, 18.2)

ACPA: anti-citrullinated protein antibody, ADR: adverse drug reaction, csDMARDs: conventional synthetic disease modifying antirheumatic drugs, DAS-28: Disease Activity Score 28 joint count, DREAM-RA: Dutch Rheumatoid Arthritis Monitoring registry, MST: Medisch Spectrum Twente, Enschede, the Netherlands, RF: rheumatoid factor

such as dyspnea). Table A and Table B in the Annex give an overview of the nature of ADRs per PT according to MedDRA terminology as well.

The number of serious ADRs per SOC are shown by asterisks (*) in Table 2. For ADA, pericarditis and pneumonia were considered serious ADRs 1 and 2 times respectively, all resulting in (prolonged) hospitalization. For ETN, bacterial arthritis, a localized infection and sepsis were considered serious ADRs, all resulting in (prolonged) inpatient hospitalization and considered life-threatening once (sepsis).

Table 2. First-time ADRs experienced by bDMARD-naïve MST DREAM-RA patients treated with adalimumab and etanercept. The asterisks (*) indicate the number of ADRs registered as serious.

SOC	% (N)
Adalimumab (57 patients, 73 ADRs)	
Skin and subcutaneous tissue disorders	24.7% (18)
Infections and infestations	16.4% (12)*
General disorders and administration site conditions	9.6% (7)
Gastrointestinal disorders	8.2% (6)
Investigations	8.2% (6)
Nervous system disorders	8.2% (6)
Respiratory, thoracic and mediastinal disorders	6.8% (5)
Neoplasms benign, malignant and unspecified	4.1% (3)
Blood and lymphatic system disorders	2.7% (2)
Musculoskeletal and connective tissue disorders	2.7% (2)
Psychiatric disorders	2.7% (2)
Cardiac disorders	1.4% (1)*
Ear and labyrinth disorders	1.4% (1)
Eye disorders	1.4% (1)
Renal and urinary disorders	1.4% (1)
Etanercept (33 patients, 39 ADRs)	
Infections and infestations	20.5% (8)***
General disorders and administration site conditions	15.4% (6)
Respiratory, thoracic and mediastinal disorders	15.4% (6)
Nervous system disorders	10.3% (4)
Skin and subcutaneous tissue disorders	10.3% (4)
Gastrointestinal disorders	7.7% (3)
Blood and lymphatic system disorders	5.1% (2)
Investigations	5.1% (2)
Musculoskeletal and connective tissue disorders	2.6% (1)
Neoplasms benign, malignant and unspecified	2.6% (1)
Reproductive system and breast disorders	2.6% (1)
Vascular disorders	2.6% (1)

ADRs: adverse drug reactions, bDMARD: biological disease-modifying antirheumatic drugs, DREAM-RA: Dutch Rheumatoid Arthritis Monitoring registry, MST: Medisch Spectrum Twente, Enschede, the Netherlands, SOC: System Organ Class

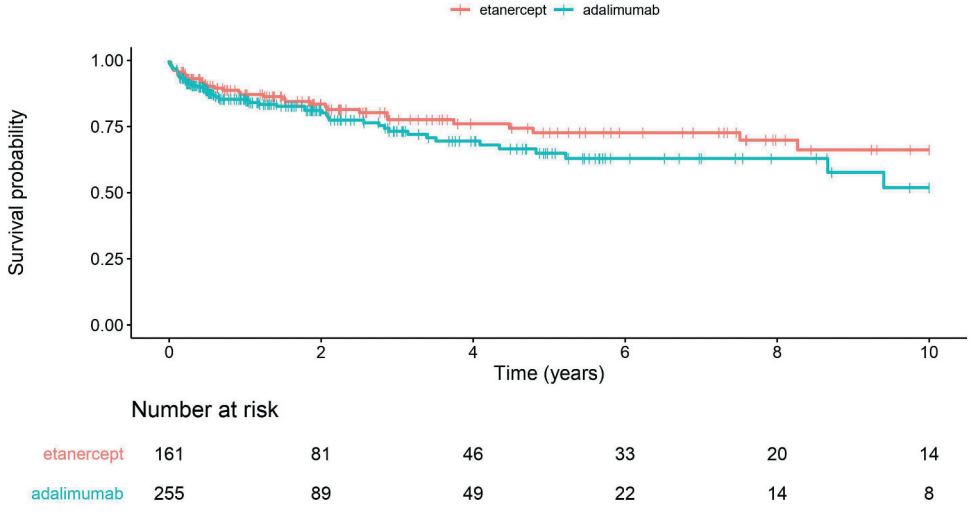

Figure 2. Kaplan–Meier of time to first ADR up to 10 years treatment for DREAM-RA patients treated with adalimumab and etanercept in MST hospital (years). Time to first ADR for treatment with etanercept (ETN) and adalimumab (ADA) are shown. Vertical dashes indicate censored data. ADR: adverse drug reaction, DREAM-RA: Dutch Rheumatoid Arthritis Monitoring registry, MST: Medisch Spectrum Twente, Enschede, the Netherlands.

3.2. Time to first adverse drug reaction and drug survival

Figures 2 and 3 show Kaplan–Meier curves of time to first ADR and drug survival up to 10 years of both treatments. The figures show the number of patients at risk of experiencing a first ADR and treatment discontinuation, respectively, up to 10 years of treatment with ADA and ETN.

3.2.1. Cox proportional hazards models

The proportional hazards assumption was met for time to first ADR and drug survival (unadjusted models p = 0.583 and p = 0.970, respectively; adjusted models p = 0.226 and 0.588, respectively). For 10 years survival, the crude HR for time to first ADR for ADA vs ETN was 1.34 (95% CI [0.87–2.06], p = 0.182). When adjusted for age at start, gender and concomitant csDMARD use,

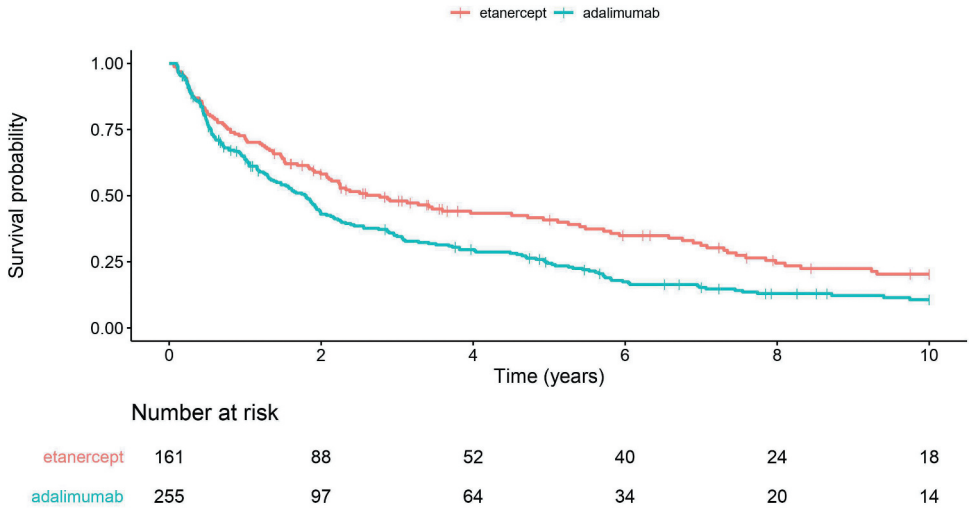

Figure 3. Kaplan–Meier of drug survival up to 10 years for DREAM-RA patients treated with adalimumab and etanercept in MST hospital (years). Drug survival of treatment with etanercept (ETN) and adalimumab (ADA) are shown. Vertical dashes indicate censored data. DREAM-RA: Dutch Rheumatoid Arthritis Monitoring registry, MST: Medisch Spectrum Twente, Enschede, the Netherlands.

the HR was 1.40 (95% CI [0.91–2.17], p = 0.129). The crude HR for drug survival for ADA vs ETN was 1.45 (95% CI [1.15–1.83], p = 0.001). When adjusted for age at start, gender and concomitant csDMARD use, the HR was 1.59 (95% CI [1.26–2.02], p < 0.001). The full results of the adjusted Cox proportional hazards models are shown Table C in the Annex.

3.2.2. Post-hoc sensitivity analysis

We performed post-hoc sensitivity analyses for 2- and 5-year survival. For time to first ADR up to 2 years, the crude HR for ADA vs ETN was 1.21 (95% CI [0.71–2.01], p = 0.477). When adjusted for age at start, gender and concomitant csDMARD use, the HR was 1.27 [0.76–2.14], p = 0.366). For drug survival up to 2 years, the crude HR for ADA vs ETN was 1.49 (95% CI [1.10–1.99], p = 0.008). When adjusted for age at start, gender and concomitant csDMARD use, the HR was 1.63 (95% CI [1.22–2.02], p < 0.001). The complete outcomes of the models can be found in Table D in the Annex.

For time to first ADR up to 5 years, the crude HR for ADA vs ETN was 1.30 (95% CI [0.84–2.03], p = 0.241). When adjusted for age at start, gender and concomitant csDMARD use, the HR was 1.36 (95% CI [0.84–2.14), p = 0.172). For drug survival up to 5 years, the crude HR for ADA vs ETN was 1.48 (95% CI [1.15–1.91], p = 0.002). When adjusted for age at start, gender and concomitant csDMARD use, the HR was 1.62 (95% CI [1.25–2.10], p < 0.001). The complete outcomes of the models can be found in Table E in the Annex.

3.3. Share of adverse drug reactions in causes of treatment discontinuation

The causes of treatment discontinuation of 325 patients (78.1%) were assessed, the other 91 patients (21.9%) did not stop first-time treatment before 30 April 2020. Most patients (118, 36.3%) discontinued treatment because of ineffectiveness of the drug. A total of 68 patients (20.9%) discontinued treatment because of ADRs. For 70 patients (21.5%) the reason of discontinuation remains unclear. For both ADA and ETN users, the main reasons of discontinuation were ineffectiveness (ADA 73 (35.1%) and ETN 45 (38.5%) and ADRs (ADA 43 (20.7%) and ETN 25 (21.4%)) as well. Information on causes of treatment discontinuation is summarized in Table 3.

Table 3. **Causes of treatment discontinuation of first-time treatment of DREAM-RA patients treated with adalimumab and etanercept in MST hospital**. Of the 416 patients using bDMARDs, 91 patients did not stop treatment before 30 April 2020, 47 for ADA and 44 for ETN. For the resulting 325 patients that discontinued their treatment, reasons of treatment discontinuation treatment are shown below.

	Total, N (%)	Adalimumab, N (%)	Etanercept, N (%)
Causes of treatment discontinuation	325 (100)	208 (100)	117 (100)
Ineffectiveness	118 (36.3)	73 (35.1)	45 (38.5)
ADRs	68 (20.9)	43 (20.7)	25 (21.4)
Low disease activity/remission	49 (15.1)	39 (18.8)	10 (8.5)
Sufficient effect	7 (2.2)	6 (2.9)	1 (0.9)
Ineffectiveness and ADRs	6 (1.9)	2 (1.0)	4 (3.4)
Death	1 (0.31)	0 (0)	1 (0.9)
No stop reason	11 (3.4)	7 (3.4)	4 (3.4)
Other *(% of other)*	65 (20.7)	38 (18.8)	27 (23.1)
Other causes	1 *(1.5)*	0 (0)	1 *(3.7)*
Incident	3 *(4.5)*	1 *(2.6)*	2 *(7.4)*
Infection	2 *(3.0)*	2 *(5.3)*	0 *(0)*
Patients' initiative	1 *(1.5)*	1 *(2.6)*	0 *(0)*
No text	59 *(88.1)*	34 *(89.5)*	24 *(88.8)*

ADRs: adverse drug reactions, bDMARDs: biologic disease-modifying antirheumatic drugs, DREAM-RA: Dutch Rheumatoid Arthritis Monitoring registry, MST: Medisch Spectrum Twente, Enschede, the Netherlands

4. Discussion

Despite the assumed interchangeable nature of ADA and ETN, this study shows that drug survival up to 2, 5, and 10 years is significantly different for ADA and ETN after adjustment for age at start of treatment, gender and concomitant csDMARD use. In both the short and long term, ADA is more likely to be discontinued than ETN. The survival analysis of time to first

ADR did not show any differences between ADA and ETN for either 2-, 5-, or 10-year survival.

Meanwhile, the number of first-time ADRs per patient year at risk for ADA is almost double compared to ETN. The types of ADRs also differed. It is known from clinical practice that ETN is associated with less infections than ADA, possibly due to differences in characteristics of the biologicals and subsequently, the mechanism of action [23]. Even though both ADA and ETN are TNF-α inhibitors, ADA is a monoclonal immunoglobulin G subclass 1 antibody, while ETN is an Fc-fusion protein [24]. This means ADA also influences the immunological abilities of cells presenting the TNF-α receptor, while ETN does not [25,26]. This may cause patients using ADA to be more susceptible to infections compared to patients using ETN, even though the exact cause of the differences in risk for infections has yet to be determined [25,27]. As we used real-world data, HCPs may have considered these drug features when prescribing bDMARDs for patients with predisposing factors for infections and probably initiated ETN instead of ADA when risk factors were present. Despite the differences in ADR profile and risk of experiencing an ADR, ADRs do not appear to be the cause of differences in drug survival. This is in line with the results on causes of treatment discontinuation that show the influence of ADRs is similar for both ADA and ETN.

To the best of our knowledge, no previous survival analysis studies have been performed on time to first ADR, whether serious, during first-time treatment for ADA and ETN separately. However, several studies have been performed on the drug survival of ADA and ETN, from which no unequivocal conclusions can be drawn [11–13]. Some studies suggested ADA had a higher median drug survival compared to ETN [12,13]. Outcomes of another study suggested ETN to have the longest survival [11]. The latter is in line with our study, which suggests that in both short and long term, ETN has a longer drug survival compared to ADA. Discrepancies on drug survival may be caused by differences in study design and in definitions of discontinuation of drug therapy and follow-up time.

Our study was performed with real-world data from a representative patient population with a long follow-up time. Although it is generally accepted that these data sources are useful, we must also consider their limitations. First, there is a possibility of confounding by indication. Before prescribing drug treatments, HCPs will consider all patients characteristics to choose the best treatment option amongst all those available. However, the influence of confounding by indication is very hard to detect in an observational study, since not all patient-specific factors that may be of influence on treatment assignation are described in a registry. To limit the influence of confounding by indication we assessed age, gender and the available DAS28 score closest to the start of the treatments. These characteristics were comparable between the different treatment groups. Even more importantly, patients in the DREAM-RA registry were assigned to a specific treatment according to a treat-to-target protocol. Adherence to this protocol has shown to be high [17]. Second, the use of corticosteroids was not taken into consideration in this study. However, the use of supplemental corticosteroids is widespread in RA treatment and the protocol for the use of corticosteroids is the same for ADA and ETN. Therefore, it is not expected to be of influence on the comparison between ADA and ETN. A third limitation of this data source might be underreporting of ADRs due to time constraints and/or registration fatigue of HCPs. This is especially likely to be the case for non-serious and well-known ADRs. The impact of this limitation is reduced by offering patients the opportunity to record ADRs in the mijnreumacentrum.nl registry by themselves. Since HCPs must validate the patient reported ADRs before these are captured in the registry, differences in perspective of patients and HCPs may have caused possible ADRs to be lost. Altogether, the opportunity for patients to report ADRs has likely contributed to better registration of ADRs and potential under recording can be expected to apply evenly for both bDMARDs.

5. Conclusions

This is the first study comparing frequencies and nature of ADRs, time to first ADR, drug survival and causes of treatment discontinuation between the most used bDMARDs in a real-life cohort of RA patients during first-time treatment periods. Our study shows that the frequency of ADRs seems to be higher for ADA and ADA is more likely to be discontinued compared to ETN up to 2-, 5-, and 10-year drug treatment. However, time to first ADR during first-time treatment does not differ. ADRs seem to be a major, but not only, reason for discontinuation of treatment.

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Declaration of interests

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Author contribution statement

All authors were involved in the conception and design of the study. K Velthuis and NT Jessurun, researched, analyzed, and interpreted the data. All authors critically reviewed and revised the paper for intellectual content, provided detailed feedback, read an approved the final manuscript, agreed to be accountable for all aspects of the work and have agreed on submitting the manuscript.

Ethics statement

The DREAM protocols were approved by the institutional medical ethics committee review board of participating hospitals and informed consent was obtained from all patients. For this specific study, no further ethical approval was required according to Dutch law.

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