Drug survival and predictor factors for discontinuation of first-line biologic therapy in rheumatoid arthritis: data from a real-world single-centre study

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Abstract

Objective

To evaluate the survival of the first biological disease-modifying anti-rheumatic drug (bDMARD) in a Greek rheumatoid arthritis (RA) cohort and determine factors influencing drug retention rates.

Methods

Patients from the Pathophysiology Clinic of LAIKON University Hospital who received their first bDMARD were stratified into anti-tumour necrosis factor (anti-TNF) and non-anti-TNF groups, and whether an event occurred. An event was defined as discontinuation due to inefficacy or adverse event (AE), including severe infections. Drug survival curves were calculated using the Kaplan-Meier method. Analysis was performed using t-tests, chi-square tests, and Cox proportional hazards in STATA, with a 5% significance level.

Results

We included 724 patients, mostly females (79%), with a median age of 48.6 ±15.7 years at diagnosis. More than half were positive for RF and/or ACPA, with a baseline DAS28-ESR of 4.9 ±1.5. The most used anti-TNFs were etanercept (n=261), infliximab (n=177), adalimumab (n=148), while rituximab (RTX, n=40) was the most used non-anti-TNF. RTX recipients experienced one-half of the events compared to those in the anti-TNF group (IRR 0.52, 95%CI: 0.27 to 0.92). After 276 months, 223 patients discontinued treatment due to inefficacy and 187 due to AEs. Most withdrawals (73.3%) occurred within the first 50 months regardless of cause. RTX was found to be protective against treatment failure, while both RF and ACPA positivity were identified as potential risk factors for discontinuation due to either failure or AE.

Conclusion

Only 26.7% of patients remained on first bDMARD after 50 months, with those receiving RTX less likely to discontinue for any reason. RF and/or ACPA positivity could be potential risk factors for discontinuation due to AEs or inefficacy.

Key words

rheumatoid arthritis, rituximab, anti-tumour necrosis factor, rheumatoid factor, anti-citrullinated protein antibodies

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease affecting approximately 1% of the general population. It is characterised by synovial joint inflammation, leading to progressive cartilage destruction and permanent joint damage. However, RA is also a systemic disease with a multitude of extra-articular manifestations and co-existing conditions, leading to significant morbidity and premature mortality (1).

In 2020, an estimated 17.6 million people suffered from RA worldwide. The presence of multiple options in our treatment quiver has led to a 23.8% reduction in mortality over the past three decades (2). It is estimated that 31.7 million people will have RA worldwide by 2050, highlighting the necessity of global awareness regarding the significance of early diagnosis and appropriate treatment (3).

In recent decades, there has been a significant change in the treatment of RA with the introduction of biologic (bDMARDs) and targeted synthetic DMARDs (tsDMARDs). These drugs are used when conventional DMARDs (cDMARDs) fail to control the disease (4). Lack of sufficient head-to-head studies comparing bDMARDs makes the choice of the first bDMARD a matter of 'trial-and-error', leading to continued exposure of patients to drugs that either do not respond or have unnecessary side effects. Currently, advancements in multi-omics, bioinformatics, and biostatistics enable the identification of biomarkers for patient stratification, facilitating the prediction of therapeutic responses and the elucidation of the molecular basis associated with each drug failure (4-6). However, the results still need to be conclusive (7).

Previous studies have shown that 50% of RA patients discontinue the first anti-tumour necrosis factor (anti-TNF) due to 4 different scenarios: a) primary failure, indicating an inappropriate mechanism of action for the specific RA subtype; b) secondary failure due to the development of anti-drug antibodies, potentially affecting its efficacy and safety profile, c) partial efficacy, not sufficient to achieve treatment goal - remission or low disease activity (LDA), d) occurrence of adverse events (AEs) (8). Therefore, identifying factors related to longer drug survival and, thus, better outcomes are crucial (9).

This study aimed to evaluate the survival of the first bDMARD in a Greek real-world cohort of RA patients and to determine the factors influencing drug retention rates, hoping to pave the way for better patient outcomes and a more optimistic future for RA treatment.

Patients and methods

Population and study design

We conducted a retrospective cohort study of patients with a final diagnosis of RA from the patient records of the Pathophysiology Clinic of 'LAIKON', General Hospital of Athens, who were followed up at the Outpatient Rheumatology Department of the Clinic between October 1985 and March 2021. Patients aged ≥18 years old who met the 2010 ACR/EULAR classification criteria for RA and had received at least one dose of their first bDMARD treatment were included in this study.

The records of 1910 adults with a final diagnosis of RA were initially selected, and detailed information on various variables was recorded. After excluding those not treated with bDMARDs, 724 adults (154 men and 570 women) were included following the principles of the Declaration of Helsinki. The study protocol was approved by the Bioethics and Ethics Committee of the Medical School of the National and Kapodistrian University of Athens and the Scientific Council of the General Hospital of Athens LAIKON.

bDMARDs exposure

First-line bDMARDs were classified into two groups: the anti-TNF group (n=622), which included infliximab, adalimumab, etanercept, other combined anti-TNFs due to the small numbers of patients treated with them (golimumab, certolizumab pegol) and non-anti-TNF (n=102), which included anakinra, rituximab, tocilizumab, abatacept, others (anti-IL10, tofacitinib). Conventional DMARD combination therapy was determined if they were already taking cDMARDs and continued to do so after bDMARD initiation.

Study outcome

Discontinuation of bDMARDs was defined as interruption lasting more than 90 days or when therapy with another bDMARD was initiated. This occurred for the following reasons: We used washout rather than half-lives as a criterion. The washout of biologic drugs used for the treatment of RA varies from 28 days for etanercept (10) to over 90 days for rituximab (11). Therefore, for less than 90 days after drug discontinuation, it was not clear whether events occurring (either related to adverse effects or to some degree of therapeutic benefit) could certainly be attributed to the drug. In addition, short-term drug interruptions occurred, albeit rarely, due to infections, surgery procedures, or even temporary loss of patient insurance coverage. Besides, discontinuation, defined as a 90-day interval lasting drug interruption, has been used in other RA studies (10-12). For rituximab, discontinuation was defined as interruption lasting more than one year due to the prolonged drug biological activity.

Discontinuing a bDMARD either due to failure or an adverse event was described as an event. The period between the bDMARD initiation date and the event was calculated for each bDMARD-treated patient and defined as the drug survival time. The severity of AEs was classified according to the Common Terminology Criteria for AEs (CTCAE v. 5.0).

Assessment of covariates

For all patients, the following data were collected before initiation of the first bDMARD: demographic information (age, sex, smoking status), comorbidities (cardiovascular disease, diabetes mellitus, dyslipidaemia, osteoporosis, autoimmune disease, cancer), age at RA diagnosis, disease duration before bDMARD treatment, extra-articular manifestations (interstitial lung disease, sicca syndrome), evidence of radiographic hand erosions, concomitant cDMARD and autoantibody status such as rheumatoid factor (RF) and anti-citrullinated antibodies (ACPA).

Disease activity was measured according to the Disease Activity Score 28 joint count assessment-Erythrocyte Sedimentation Rate (DAS28-ESR) at bDMARD initiation and at each visit until the end of the follow-up.

Statistical analysis

Baseline characteristics and laboratory variables are presented by treatment group as means and standard deviations (SD) for continuous variables and frequencies and percentages for categorical variables. T-tests and χ^2 tests were applied to assess differences in means and proportions between treatment groups. Total and individual events (first AE or failure) are recorded by the treatment group.

Incident rates (IR) of AEs or failures, along with 95% confidence intervals (95%CI), are presented as events per 1000 person-months (PM). The corresponding incident rate ratios (IRRs) were calculated based on the time from the initiation of the bDMARD until the first event occurred during follow-up. IRs were presented separately for each treatment group and each bDMARD.

Kaplan-Meier (KM) plots were applied to assess the association between the treatment group (or the specific bDMARD) and the risk of first AE, failure, or any of the two. Due to the apparent superiority of rituximab compared to the remaining non-Anti-TNF bDMARDs, the subsequent analyses were performed comparing three treatment groups, anti-TNF bDMARDS *vs*. non-anti-TNF bDMARDs (excluding rituximab) *vs*. rituximab only. KM plots were further applied by combined RF and ACPA categories. The curves were compared via the log-rank or Wilcoxon tests, giving larger weights to early events.

Initially, sex- and age-specific Cox proportional-hazards analyses were performed, and hazard ratios (HR) and corresponding 95%CIs were estimated for the two or three treatment groups (rituximab separately) plus one factor at a time. Only factors with a *p*-value <0.2 were subsequently qualified for the final model, along with sex and age at diagnosis, to control for potential confounding variables. In all models, the length of follow-up (in months), until the first AE/failure was the primary time variable, and patients without the event, were censored at the end of their follow-up period. Moreover, the time to experience the first AE or failure was examined separately. The proportional hazards assumption was evaluated through the Schoenfeld residuals using the saturated model and alternatively including the 2-treatment group variable or the 3-treatment group variable. It was found that the assumption was not violated (global *p*-value = 0.303 and 0.377, respectively). Data were analysed using STATA (Stata/SE 13.0. for Windows; Stata Corporation, College Station, TX, USA), and the level of 5% was set for statistical significance.

Results

Patient characteristics

Between October 1985 and March 2021, 1910 adult patients with a final diagnosis of RA were followed up at the Outpatient Rheumatology Department of our Clinic. Of these, 1186 not treated with bDMARDs were excluded. The final cohort included 724 RA patients who received at least one dose of their first bDMARD. The demographic, clinical characteristics and comorbidities of the patients are summarised in Table I. The study population was predominantly female (570, 79%), with a median age at diagnosis of 48.6 ±15.7 years. Most patients were non-smokers (505, 70%), while the remaining were either active (169, 23%) or ex-smokers (50, 7%). Thirty-eight patients (5%) had a second-degree family history of RA. The most prevalent comorbidity was cardiovascular disease (215, 30%), followed by dyslipidaemia (96, 13%), osteoporosis (85, 12%) and diabetes (82, 11%). More than half of the patients were RF and/or ACPA positive (408, 56.3%), with a calculated baseline DAS28-ESR of 4.9±1.5. At initiation of bDMARD, most patients (637, 88%) received at least one cDMARD, with a median duration of administration of 33.4±52.9 months. Regarding extra-articular manifestations, 139 patients (40.4%) presented with sicca symptoms, while only 46 (6.3%) of them were diagnosed with secondary Sjögren's syndrome after a minor salivary gland biopsy. RA-related interstitial lung disease (RA-ILD) was observed in 48 (14%) enrolled patients. The most frequently used first-line anti-TNFs were etanercept (ETN, n=261),

Table I. General characteristics of 724 patients with RA taking biologic bMARD by treatment group.

	bDMARD type						
	Total 724		Anti TNF 622		Non-anti TNF 102		*p*-value*
	M	SD	M	SD	M	SD	
Age at diagnosis (years)	48.6	15.7	48.1	15.8	51.8	15.2	**0.028**
Disease duration prior to treatment	20.2	40.4	20.4	41.6	19.1	32.7	0.766
DAS28 / ESR baseline	4.9	1.5	4.9	1.5	4.9	1.5	0.993
ESR baseline	41.5	27.9	41.0	27.7	44.6	29.4	0.233
	n	**%**	**n**	**%**	**n**	**%**	
Sex							0.856
Male	570	78.7	489	78.6	81	79.4	
Female	154	21.3	133	21.4	21	20.6	
Event (discontinuation)							0.893
No	315	43.5	270	43.4	45	44.1	
Yes	409	56.5	352	56.6	57	55.9	
Comorbidities							**0.029**
No	246	34.0	221	35.5	25	24.5	
Yes	478	66.0	401	64.5	77	75.5	
CRP0							0.384
No	291	40.2	254	40.8	37	36.3	
Yes	433	59.8	368	59.2	65	63.7	
RF / ACPA							**<0.001**
RF- and ACPA-	316	43.7	288	46.4	28	27.5	
RF+ or ACPA+	215	29.7	186	30.0	29	28.4	
RF+ and ACPA+	193	26.6	148	23.6	45	44.1	
Erosions							0.157
No	709	97.9	611	98.2	98	96.1	
Yes	15	2.1	11	1.8	4	3.9	
Extra-articular manifestations							0.107
No	380	52.5	334	53.7	46	45.1	
Yes	344	47.5	288	46.3	56	54.9	
cDMARD							0.219
No	87	12.0	71	11.4	16	15.7	
Yes	637	88.0	551	88.6	86	84.3	

infliximab (INF, n=177), and adalimumab (ADA, n=148). Non-anti-TNFs were rituximab (RTX, n=40), anakinra (n=29), and tocilizumab (n=10). The median duration of treatment with the first bDMARD was 61 months (Q1:18, Q3:125).

On average, non-anti-TNF patients were older (51.8±15.2 years) compared to those receiving anti-TNF (48.1±15.8; p=0.028). A higher percentage of comorbidities (75% *vs*. 65%; p=0.029) were found in the non-anti-TNF group. Differences were also found across the combined RF and ACPA groups (p<0.001). Nearly half of the patients in the non-anti-TNF group were both RF and ACPA positive (44.1%), while almost half of the comparable treatment group (46.4%) were double negative.

Drug survival curves by bDMARD exposure status

During the first 100 months of follow-up, 91% of patients discontinued their first bDMARD for any reason (failure or AE); more specifically, 73.3% of withdrawals occurred within the first 50 months.

Incident rates and respective ratios for the first AE or failure are presented in Table II. Patients in the anti-TNF group experienced 352 events in 23,865 person-months (PM), leading to an IR of 14.75 events per 1,000 PM. The IR for the group of non-anti TNF was slightly higher (18.75), but the IRR of 1.27 did not reach statistical significance. However, when removing those treated with RTX from the non-anti TNF group, patients receiving any other non-anti TNF bDMARD experienced twice more events compared to the reference group (2.06, 95%CI: 1.48 to 2.82). On the contrary, in the RTX group, only 12 events occurred in 1,559 PM, leading to an IR of 7.70 events per 1,000 PM. Those receiving RTX had half the rate of events compared to the anti-TNF group (IRR 0.52, 95%CI: 0.27 to 0.92). When comparing specific bDMARDs using INF as a referent, the RTX, ADA, and ETN were found to have a significantly lower rate of events.

Drug survival curves by causes of discontinuation

After a 276-month follow-up, 223

Table II. Incident rates of AE/failure per 1,000 person-months and incident rate ratios.

	PM for first AE/failure	No. of events	IR per 1000 pm	95% CI for IR			IRR	95%CI for IRR
Anti-TNF	23865	352	14.75	13.29	to	16.37	reference	reference
Non-anti-TNF	3040	57	18.75	14.46	to	24.31	1.27	0.94 to 1.69
Non-anti-TNF (excl. Rituximab)	1481	45	30.38	22.69	to	40.70	2.06	**1.48 to 2.82**
Rituximab	1559	12	7.70	4.37	to	13.55	0.52	**0.27 to 0.92**
Infliximab	6539	143	21.87	18.56	to	25.76	reference	reference
Adalimumab	6607	75	11.35	9.05	to	14.23	0.52	**0.39 to 0.69**
Etanercept	9876	112	11.34	9.42	to	13.65	0.52	**0.40 to 0.67**
Anakinra	883	23	26.05	17.31	to	39.20	1.19	0.73 to 1.86
Rituximab	1559	12	7.70	4.37	to	13.55	0.35	**0.18 to 0.63**
Tocilizumab	202	6	29.70	13.34	to	66.12	1.36	0.49 to 3.03
Abatacept	182	4	21.98	8.25	to	58.56	1.00	0.27 to 2.63
Other	1057	34	32.17	22.98	to	45.02	1.47	0.98 to 2.15

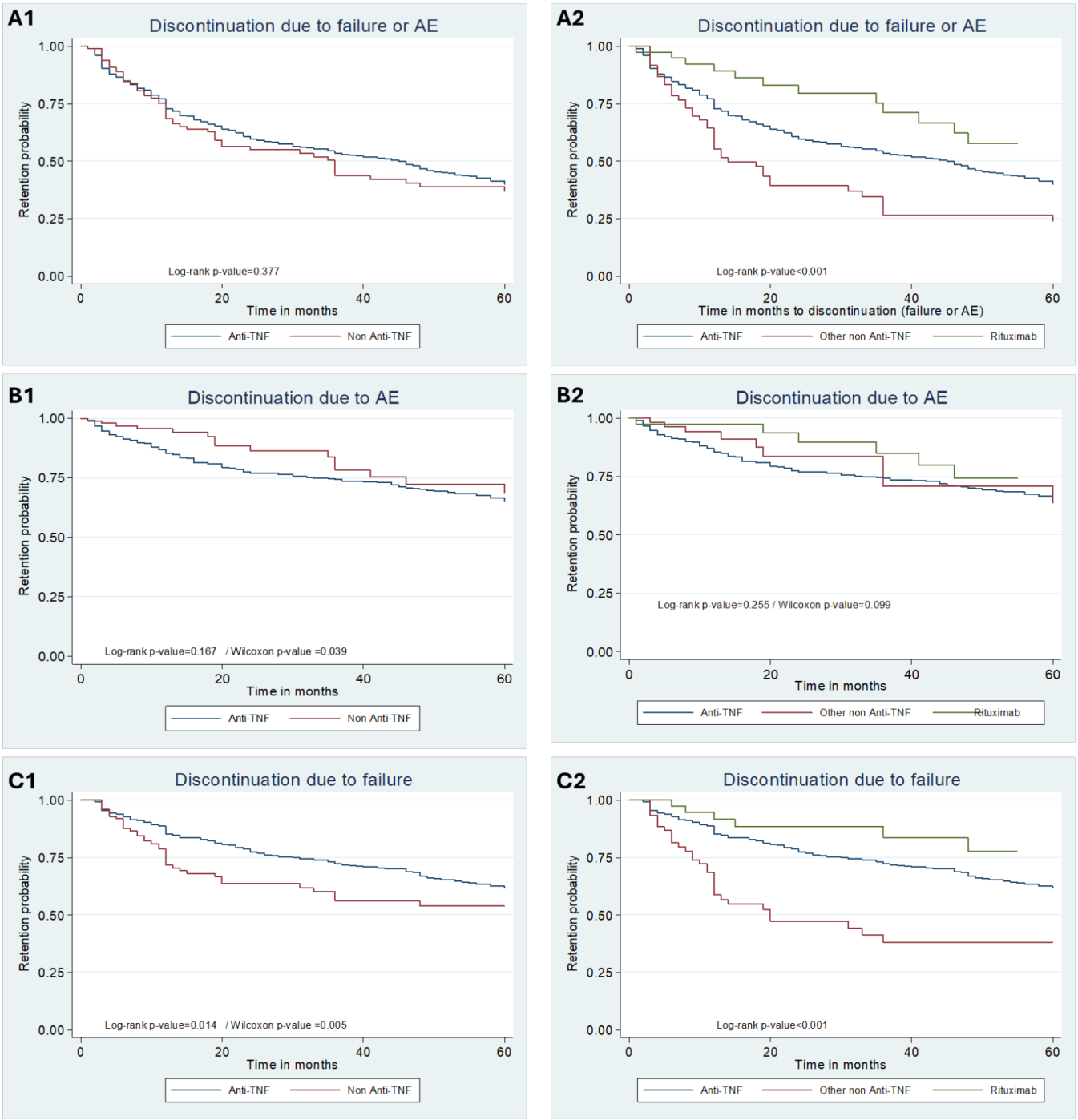

Fig. 1. Kaplan-Meier plots for risk of AE or failure (**A**), AE only (**B**), and failure only (**C**) comparing 1) anti-TNFs *vs*. non-anti TNFs including rituximab and 2) anti-*TNFs vs*. rituximab *vs*. other non-anti TNFs.

patients (54.4%) discontinued treatment due to inefficacy and 187 (45.7%) due to AEs.

Figure 1 presents the Kaplan-Meier survival curves – where survival refers to drug retention without AE or failure – comparing the anti-TNF *vs*. non-anti-TNF (including RTX) treatment groups (left column: A1, B1, and C1) or anti-TNF *vs*. RTX *vs*. other non-anti TNFs (right column: A2, B2, and C2). Figures with letter A analyse time to first AE or failure (all events); letter B refers to time to first AE only, and letter C refers to time to first failure only. Comparing the two treatment categories (anti-TNFs *vs*. non-anti-TNFs), the curves do not differ significantly regarding time to either AE or failure (A1; p=0.377). However, comparing the probability of retention without any AE only, there seems to be a lower risk of AEs for those treated with non-anti-TNFs, including RTX (B1; Wilcoxon p=0.039). On the contrary, the risk of early failure was significantly higher among the non-anti-TNF-treated patients (C1; p=0.005). Focusing on RTX (right column), the risk of any event is substantially lower. In comparison, the

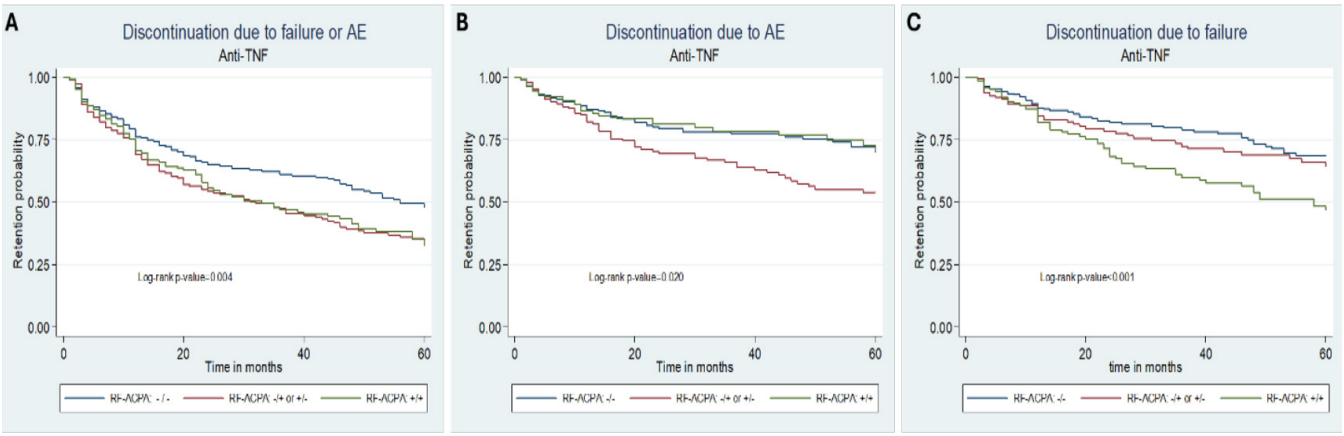

Fig. 2. Kaplan-Meier plots of drug retention probability for anti-TNF treatment group by RF and ACPA combined groups. **A**) for time AE or failure, (**B**) for time to AE only, and (**C**) for time to failure only.

risk of failure is higher for those receiving any other non-anti-TNF treatment. The median survival for AE or failure was 45 months for the anti-TNF group and 14 months for the other non-anti-TNFs (A2), while more than 50% of those treated with RTX remained without event after 50 months of treatment.

Survival curves by RF and ACPA autoantibody status

Regarding seropositivity status and drug retention in treatment groups, experiences of any event (AE only, or failure only) for the combined RF and ACPA groups are presented in Figure 2 for the Anti-TNF group. Both RF and ACPA negativity combined were associated with a higher retention probability (p=0.004). Those with both RF and ACPA positivity experienced a higher risk of failure (p<0.001), while the group with either one autoantibody-positive experienced a higher risk of AEs. No differences in survival curves occurred among the non-anti-TNF groups or RTX (data not shown).

Risk factors of discontinuation

Table III presents the hazard ratios (HRs) and 95%CIs from the multivariate Cox regression models, analysing the time to first AE/failure, time to first AE only, and time to first failure only alternatively. Only variables that met the criterion of p<0.2 are presented in each alternate time to event analysis. When time to any event is considered, treatment with RTX had the lowest risk of AE or failure compared to other drugs (HR=0.45, 95%CI: 0.25 to 0.82) and after controlling for the other factors. RF and/or ACPA positivity, concomitant cDMARD, and, to a lesser extent, age were independent risk factors of AE or failure occurrence. Considering discontinuation due to AE only the positivity of either RF or ACPA (but not both) and concomitant cDMARD were also identified as potential risk factors, while smoking was a protective factor (HR=0.68, 95%CI: 0.46 to 0.98). The risk of AE was lower for RTX-treated patients, but it did not reach statistical significance. When discontinuation due to treatment failure is considered, RTX had a protective effect (HR=0.38, 95%CI: 0.17 to 0.87), and both RF and ACPA positivity were identified as potential risk factors (HR=1.67, 95%CI: 1.21 to 2.31, p=0.002). At the same time, those treated with any other non-anti-TNF had more than twice the risk of failure compared to those treated with anti-TNFs (HR=2.32, 95%CI: 1.60 to 3.37).

Discussion

In this real-world retrospective cohort study, we evaluated the survival of the first bDMARD and the factors influencing drug retention rates in a Greek RA population. We demonstrated that RTX-treated patients had half the rate of discontinuations due to failure or AEs, and more than 50% of those treated with RTX remained without event after 50 months of treatment. Using INF as a referent, the RTX, ADA, and ETN were found to have a significantly lower rate of events. Patients treated with non-anti-TNFs, including RTX, appeared to have a lower risk of early AE, while those treated with anti-TNF had a lower risk of early failure. Focusing on RTX, the risk of any event is substantially lower for those being treated with.

An important question in the literature is whether RTX is ideal as a first-line bDMARD for RA. In 2006, RTX was approved for patients with severe active RA who have not responded adequately to an anti-TNF therapy (13). However, several patients receive RTX as their first bDMARD in clinical practice, mainly due to comorbidities that preclude anti-TNF use. Since 2008, McGonagle *et al*. concluded that first-line RTX therapy is reasonable if anti-TNFs are unavailable or there are relevant contraindications to their use (14). Nevertheless, only a few studies have investigated the long-term effect of RTX, mainly due to variability in the frequency of administration and dosing intervals (15).

In a multicentre study of long-term RTX persistence in patients with RA, 65% of bDMARD-naive patients remained on RTX therapy after 4 years, while prior bDMARD use was not significantly associated with RTX discontinuation (16). Conversely, a retrospective study of 404 RA patients who received RTX at University College London Hospitals from 1998 until 2020 showed that RTX survival was lower in seronegative patients and those who had previously failed at least one bDMARD (17).

In our cohort, 40 patients received RTX

Table III. Effect estimate (HR) and 95%CI for the risk of AE and/or failure in RA patients treated with bDMARDs.

Variables	Discontinuation due to AE or failure				Discontinuation due to AE				Discontinuation due to failure			
	HR	95% CI		*p*-value	HR	95% CI		*p*-value	HR	95% CI		*p*-value
Treatment group												
Anti-TNF	ref				ref				ref			
Non-Anti-TNF (other)	1.64	1.20	2.25	**0.002**	0.84	0.45	1.55	0.570	2.32	1.60	3.37	**<0.001**
Rituximab	0.45	0.25	0.82	**0.008**	0.55	0.24	1.26	0.159	0.38	0.17	0.87	**0.022**
Sex												
Female	ref				ref				ref			
Male	0.97	0.76	1.24	0.806	1.11	0.78	1.58	0.556	0.85	0.61	1.20	0.357
Age at diagnosis	1.01	1.00	1.01	*0.096*	1.01	1.00	1.02	0.190	1.00	1.00	1.01	0.326
Comorbidities												
No	ref				ref				Not qualified			
Yes	1.08	0.85	1.36	0.545	1.31	0.90	1.91	0.157				
DAS28/ESR0	1.05	0.97	1.13	0.248	1.11	0.99	1.24	*0.085*	Not qualified			
CRP0												
No	ref				ref				Not qualified			
Yes	1.13	0.90	1.42	0.283	1.15	0.82	1.60	0.417				
Concomitant cDMARD												
No	ref				ref				Not qualified			
Yes	1.41	1.01	1.97	**0.042**	1.80	1.04	3.12	**0.035**				
RF/ACPA												
- -	ref				ref				ref			
- + / + -	1.29	1.02	1.63	**0.034**	1.42	1.01	1.99	**0.044**	1.15	0.82	1.60	0.414
+ +	1.35	1.06	1.73	**0.016**	1.02	0.69	1.51	0.910	1.67	1.21	2.31	**0.002**
Smoke												
No	Not qualified			ref					ref			
Yes				0.68	0.46	0.98	**0.039**		1.21	0.90	1.62	0.211
Extra-articular manifestations												
No	Not qualified			ref					Not qualified			
Yes					1.17	0.85	1.61	0.335				
Erosions												
No	Not qualified				Not qualified				ref			
Yes									1.99	0.93	4.25	*0.074*

as their first bDMARD. Among these, 30 were suffering from either comorbidities that contraindicated anti-TNF usage – including a history of solid cancer (n=10), lymphoma (n=1), RA-ILD (n=5), Sjögren syndrome (n=5), and multiple sclerosis (n=1) – or they tested ANA positive (n=8), making anti-TNF treatment problematic. The remaining 10 patients had extremely high autoantibody titres (RF and ACPA) and higher disease activity. Given these patients' elevated B-cell activation levels, we used RTX as their first bDMARD.

Our study showed that both RF and ACPA negativity combined had a higher anti-TNF retention probability without any event. In contrast, those with both RF and ACPA positivity had a higher risk of failure. No differences in survival occurred among the non-anti-TNF groups or RTX alone, probably due to the small number of patients. Since seronegative RA typically exhibits fewer bone erosions, structural damage, and a milder disease course, we hypothesised that these patients may respond more favourably.

RF and ACPA autoantibodies have a direct pathogenic role in RA progression and appear to be valuable clinical predictors of drug survival. Some studies have suggested that RF or ACPA antibody status is associated with clinical response to anti-TNF therapy, whereas others found no such association (18, 19). To date, no definite conclusion has been reached.

A meta-analysis of 14 studies involving 5561 RA patients found no association between the presence of RF and response to anti-TNF treatment, with a pooled relative risk of 0.98 (95% CI: 0.91–1.05, p=0.54). Similarly, the presence of ACPAs was also not associated with patient response, with a pooled RR of 0.88 (95% CI of 0.76–1.03, p=0.11), suggesting a potential association between the absence of ACPA and a response to anti-TNF therapy. Overall, the combined results did not conclusively support or refute the relationship between the RF and/or ACPA positivity and the effectiveness of anti-TNF treatment (18). Contrariwise, in an exploratory analysis of the 2-year AMPLE study, higher baseline anti-cyclic citrullinated peptide-2 (CCP2) concentration was linked to better DAS28 and HAQ-DI responses, as well as higher rates of CDAI and SDAI remission with Abatacept, but not with Adalimumab, in the background of methotrexate (MTX) (19). Julià *et al*. reported that the concurrent presence of RF and anti-CCP was associated with more favourable

outcomes than the presence of either autoantibody alone (20).

Furthermore, Nakayama *et al*. found that Certolizumab pegol, which does not contain an Fc fragment, may be more effective than anti-TNFs containing Fc in RA patients with high RF titres (21).Conversely, in a recent retrospective cohort study, Kaplan *et al*. demonstrated that RF titres significantly impacted the effectiveness of anti-TNF therapies, while the presence of the Fc fragment did not (22).

Considering discontinuation attributable solely to AEs, we identified RF or ACPA positivity and concurrent use of cDMARD as potential risk factors in our study. Meanwhile, smoking appeared to be a protective factor.

Some bDMARDs are associated with immunogenicity that might be attenuated with the concomitant use of MTX. Around 13% of patients show positive anti-drug antibodies to anti-TNF, which varies depending on the specific anti-TNF used (23). According to 2022 EULAR recommendations, a csDMARD, particularly MTX, should be initiated upon diagnosing RA to achieve remission or LDA. If remission is not achieved and RA presents poor prognostic factors, a bDMARD is added to the csDMARD. Combining csDMARD and bDMARD is more effective than bDMARD monotherapy (24). However, the impact of combination therapy on the risk of side effects compared with bDMARD monotherapy has yet to be clearly evaluated.

Lampropoulos *et al*. concluded that patients using bDMARDs had a significantly higher risk of AEs than those using csDMARDs, with an adjusted HR of 1.98. Additionally, higher doses of MTX did not increase the risk for AEs. This study compared bDMARDs with csDMARDs but did not study the risk between bDMARDs in combination with csDMARDs and monotherapy (25). Tarp *et al*. indicated that combination therapy increases the likelihood of achieving ACR50 responses by around 32% compared to bDMARD monotherapy after 6 months. The overall estimate of discontinuing therapy due to AEs from the concomitant use of MTX was 1.27, suggesting a possible 20% increased risk compared to bDMARD monotherapy, corresponding to 1 more out of 100 patients (26).

On the contrary, Baratad *et al*. reported no significant difference in the occurrence of serious AEs between bDMARDs monotherapy and bDMARDs with MTX. However, an increased risk of gastrointestinal AEs has been reported with the combined therapy (27). According to the recent Spanish experts' document on using MTX in combination with bDMARDs or tsDMARDs in RA patients, the risk management for combining therapies should align with that of their individual components (28).

Smoking is a recognised risk factor for developing RA, particularly in genetically predisposed individuals with ACPA positivity. In our study, a significant portion of smokers (87, 51.5%) received non-anti-TNF treatments, which seem to demonstrate a lower risk of AEs (p=0.039). This might explain our observation.

Moreover, we have demonstrated that both RF and ACPA positivity are potential risk factors for discontinuation due to inefficacy. Furthermore, our study indicates that RTX is protective in this scenario.

Double autoantibody-positive patients seem to be characterised by a more inflammatory phenotype and, thus, a worse disease course. A study of 1,488 RA patients from the US showed that compared to the double negative (as well as each single positive) subgroup, the ACPA+/RF+ subgroup had higher disease activity, serum CRP, and inflammatory cytokines (p<0.001) (30).

Besides the inflammatory process, a potential direct role of ACPAs in promoting nociceptive mechanisms and clinical evidence suggesting that ACPA-positive RA patients may experience joint pain even in the absence of synovitis may contribute to patient failure in treatment (31).

In the literature, both RF and ACPA are recognised as significant factors influencing remission outcomes (32). Specifically, RF mainly predicts lower probabilities of achieving and sustaining remission on treatment (33, 34), while ACPA represents a significant obstacle to safe drug discontinuation (35-37).

While the autoantibody profile seems questionable in response to csDMARDs (38, 39), autoantibody-positive patients with higher B cell population activation levels are more likely to show greater response to B cell depletion, IL-6 targeting, or inhibition of T cell costimulation therapies (19, 40, 41).

Our study had several limitations. Firstly, the distribution of patients across different treatment groups was not equal. However, this also reflected the prescribing behaviour of rheumatologists in real-world studies and the limited choice of bDMARDs in the initial years. Secondly, bDMARD discontinuation was attributed to diverse factors. Reclassifying patients for whom targeted therapies have exhibited limited efficacy in primary and secondary failure is necessary. Furthermore, a multitude of adverse events resulted from various causes. An in-depth analysis of our cohort is imperative to elucidate the precise factors leading to drug discontinuation. Finally, the study's retrospective design made gathering data from patient files challenging. As a result, we could not calculate the amount of glucocorticosteroids for each patient, potentially affecting drug survival times. Additionally, there was a lack of available data on pack-years of smoking and somatometric characteristics of patients, which could also impact survival times.

In conclusion, this real-world single-centre study showed that after 50 months of follow-up, only 26.7% of patients remained on their first bDMARD. Notably, patients receiving RTX were significantly less likely to discontinue treatment for any reason. Both RF and ACPA negativity were associated with a higher likelihood of retaining anti-TNF treatment. In contrast, those patients with both RF and ACPA positivity had a greater risk of failure. Our analysis indicated that RF and/ or ACPA positivity could be potential risk factors for bDMARD discontinuation due to AEs or inefficacy. We argue that these findings are useful tools to guide clinical practice in the emerging era of personalised therapies.

References

1. GRAVALLESE EM, FIRESTEIN GS: Rheumatoid arthritis - Common origins, divergent mechanisms. *N Engl J Med* 2023; 388(6): 529-42. https://doi.org/10.1056/nejmra2103726
2. AL MAINI M, ADELOWO F, AL SALEH J *et al*.: The global challenges and opportunities in the practice of rheumatology: white paper by the World Forum on Rheumatic and Musculoskeletal Diseases. *Clin Rheumatol* 2015; 34(5): 819-29. https://doi.org/10.1007/s10067-014-2841-6
3. GBD 2021 RHEUMATOID ARTHRITIS COLLABORATORS: Global, regional, and national burden of rheumatoid arthritis, 1990-2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. *Lancet Rheumatol* 2023; 5(10): e594-e610. https://doi.org/10.1016/S2665-9913(23)00211-4
4. THOMAS J, BANSBACK N, BARBER C, WELLS G, HAZLEWOOD G: Personalized medicine in rheumatoid arthritis: combining biomarkers and patient preferences to guide therapeutic decisions. *Best Pract Res Clin Rheumatol* 2022; 36(4): 101812. https://doi.org/10.1016/j.berh.2022.101812
5. WANG Z, HUANG J, XIE D, HE D, LU A, LIANG C: Toward overcoming treatment failure in rheumatoid arthritis. *Front Immunol* 2021; 12: 755844. https://doi.org/10.3389/fimmu.2021.755844
6. D'ORAZIO A, CIRILLO AL, GRECO G *et al*.: Pathogenesis of rheumatoid arthritis: one year in review 2024. *Clin Exp Rheumatol* 2024; 42(9): 1707-13. https://doi.org/10.55563/clinexprheumatol/0307ed
7. PITZALIS C, KELLY S, HUMBY F: New learnings on the pathophysiology of RA from synovial biopsies. *Curr Opin Rheumatol* 2013; 25(3): 334-44. https://doi.org/10.1097/bor.0b013e32835fd8eb
8. FAVALLI EG, RAIMONDO MG, BECCIOLINI A, CROTTI C, BIGGIOGGERO M, CAPORALI R: The management of first-line biologic therapy failures in rheumatoid arthritis: current practice and future perspectives. *Autoimmun Rev* 2017; 16(12): 1185-95. https://doi.org/10.1016/j.autrev.2017.10.002
9. PASCUAL-RAMOS V, CONTRERAS-YÁÑEZ I, VILLA AR, CABIEDES J, RULL-GABAYET M: Medication persistence over 2 years of follow-up in a cohort of early rheumatoid arthritis patients: associated factors and relationship with disease activity and with disability. *Arthritis Res Ther* 2009; 11(1): R26. https://doi.org/10.1186/ar2620
10. BLAUVELT A, PAPP KA, GRIFFITHS CEM *et al*.: Efficacy and safety of switching to Ixekizumab in etanercept non-responders: a subanalysis from two Phase III randomized clinical trials in moderate-to-severe plaque psoriasis (UNCOVER-2 and -3). *Am J Clin Dermatol* 2017; 18(2): 273-80. https://doi.org/10.1007/s40257-016-0246-9
11. BREEDVELD F, AGARWAL S, YIN M *et al*.: Rituximab pharmacokinetics in patients with rheumatoid arthritis: B-cell levels do not correlate with clinical response. *J Clin Pharmacol* 2007; 47(9): 1119-28. https://doi.org/10.1177/0091270007305297
12. LI P, BLUM MA, VON FELDT J, HENNESSY S. DOSHI JA: Adherence, discontinuation, and switching of biologic therapies in medicaid enrollees with rheumatoid arthritis. *Value Health* 2010; 13(6): 805-12. https://doi.org/10.1111/j.1524-4733.2010.00764.x
13. COHEN SB, EMERY P, GREENWALD MW *et al*.; REFLEX TRIAL GROUP: Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum* 2006; 54(9): 2793-806. https://doi.org/10.1002/art.22025
14. MCGONAGLE D, TAN AL, MADDEN J, TAYLOR L, EMERY P: Rituximab use in everyday clinical practice as a first-line biologic therapy for the treatment of DMARD-resistant rheumatoid arthritis. *Rheumatology* (Oxford) 2008; 47(6): 865-67. https://doi.org/10.1093/rheumatology/ken103
15. KLEINER A, LOONEY RJ: Is rituximab suitable for use as a first-line biologic therapy for RA? *Nat Clin Pract Rheumatol* 2008; 4(11): 574-75. https://doi.org/10.1038/ncprheum0905
16. OLDROYD AGS, SYMMONS DPM, SERGEANT JC *et al*.; BSRBR-RA CONTRIBUTORS GROUP: Long-term persistence with rituximab in patients with rheumatoid arthritis. *Rheumatology* (Oxford) 2018; 57(6): 1089-96. https://doi.org/10.1093/rheumatology/key036
17. NORRIS-GREY C, CAMBRIDGE G, MOORE S, REDDY V, LEANDRO M: Long-term persistence of rituximab in patients with rheumatoid arthritis: an evaluation of the UCL cohort from 1998 to 2020. *Rheumatology (*Oxford) 2022; 61(2): 591-96. https://doi.org/10.1093/rheumatology/keab248
18. LV Q, YIN Y, LI X *et al*.: The status of rheumatoid factor and anti-cyclic citrullinated peptide antibody are not associated with the effect of anti-TNF-α agent treatment in patients with rheumatoid arthritis: a meta-analysis. *PLoS One* 2014; 9(2): e89442. https://doi.org/10.1371/journal.pone.0089442
19. SOKOLOVE J, SCHIFF M, FLEISCHMANN R *et al*.: Impact of baseline anti-cyclic citrullinated peptide-2 antibody concentration on efficacy outcomes following treatment with subcutaneous abatacept or adalimumab: 2-year results from the AMPLE trial. *Ann Rheum Dis* 2016; 75(4): 709-14. https://doi.org/10.1136/annrheumdis-2015-207942
20. JULIÀ A, LÓPEZ-LASANTA M, BLANCO F *et al*.: Interactions between rheumatoid arthritis antibodies are associated with the response to anti-tumor necrosis factor therapy. *BMC Musculoskelet Disord* 2021; 22(1): 372. https://doi.org/10.1186/s12891-021-04248-y
21. NAKAYAMA Y, WATANABE R, MURAKAMI K *et al*.: Differential efficacy of TNF inhibitors with or without the immunoglobulin fragment crystallizable (Fc) portion in rheumatoid arthritis: the ANSWER cohort study. *Rheumatol Int* 2022; 42(7): 1227-34. https://doi.org/10.1007/s00296-021-05086-w
22. KAPLAN H, CENGIZ G, CUCE I *et al*.: Rheumatoid factor titers, but not Fc fragments, may be strongly associated with drug survival of anti-TNF agents in patients with rheumatoid arthritis. *North Clin Istanb* 2024; 11(2): 147-57. https://doi.org/10.14744/nci.2023.01643
23. MANEIRO JR, SALGADO E, GOMEZ-REINO JJ: Immunogenicity of monoclonal antibodies against tumor necrosis factor used in chronic immune-mediated Inflammatory conditions: systematic review and meta-analysis. *JAMA Intern Med* 2013; 173(15): 1416-28. https://doi.org/10.1001/jamainternmed.2013.7430
24. SMOLEN JS, LANDEWÉ RBM, BERGSTRA SA *et al*.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Ann Rheum Dis* 2023; 82(1): 3-18. https://doi.org/10.1136/ard-2022-223356 Erratum in: *Ann Rheum Dis* 2023; 82(3): e76. https://doi.org/10.1136/ard-2022-223356corr1
25. LAMPROPOULOS CE, ORFANOS P, BOURNIA VK *et al*.: Adverse events and infections in patients with rheumatoid arthritis treated with conventional drugs or biologic agents: a real world study. *Clin Exp Rheumatol* 2015; 33(2): 216-24.
26. TARP S, JØRGENSEN TS, FURST DE *et al*.: Added value of combining methotrexate with a biological agent compared to biological monotherapy in rheumatoid arthritis patients: A systematic review and meta-analysis of randomised trials. *Semin Arthritis Rheum* 2019; 48(6): 958-66. https://doi.org/10.1016/j.semarthrit.2018.10.002
27. BARADAT C, DEGBOÉ Y, CONSTANTIN A, CANTAGREL A, RUYSSEN-WITRAND A: No impact of concomitant methotrexate use on serious adverse event and serious infection risk in patients with rheumatoid arthritis treated with bDMARDs: a systematic literature review and meta-analysis. *RMD Open* 2017; 3(1): e000352. https://doi.org/10.1136/rmdopen-2016-000352
28. TORNERO-MOLINA J, ALPERI-LÓPEZ M, CASTELLVÍ I *et al*.: Experts document on methotrexate use in combined therapy with biological or targeted synthetic disease modifying drugs in patients with rheumatoid arthritis. *Reumatol Clin* (Engl Ed) 2020 Oct 8: S1699-258x(20)30200-x. https://doi.org/10.1016/j.reuma.2020.08.003
29. CHATZIDIONYSIOU K, LUKINA G, GABAY C *et al*.: (2018). Smoking and response to rituximab in rheumatoid arthritis: results from an international European collaboration. *Scand J Rheumatol* 2018; 48(1): 17-23. https://doi.org/10.1080/03009742.2018.1466363
30. BUGATTI S, MANZO A, MONTECUCCO C, CAPORALI R: The clinical value of autoantibodies in rheumatoid arthritis. *Front Med* (Lausanne) 2018; 5: 339. https://doi.org/10.3389/fmed.2018.00339
31. WIGERBLAD G, BAS DB, FERNADES-CERQUEIRA C *et al*.: Autoantibodies to citrullinated proteins induce joint pain independent of inflammation via a chemokine-dependent mechanism. *Ann Rheum Dis* 2016; 75(4): 730-38. https://doi.org/10.1136/annrheumdis-2015-208094 Erratum in: *Ann Rheum Dis* 2019; 78(6): 865. https://doi.org/10.1136/annrheumdis-2015-208094corr1
32. MOLTENI E, ADINOLFI A, BONDI V *et al*.:

Novel insights into the management of rheumatoid arthritis: one year in review 2024. *Clin Exp Rheumatol* 2024; 42(5): 947-60. https://doi.org/10.55563/clinexprheumatol/166dsf

33. RAHEEL S, MATTESON EL, CROWSON CS, MYASOEDOVA E: Improved flare and remission pattern in rheumatoid arthritis over recent decades: a population-based study. *Rheumatology* (Oxford) 2017; 56(12): 2154-61. https://doi.org/10.1093/rheumatology/kex352
34. PAULSHUS SUNDLISÆTER N, OLSEN IC, AGA AB *et al*.; ARCTIC STUDY GROUP: Predictors of sustained remission in patients with early rheumatoid arthritis treated according to an aggressive treat-to-target protocol. *Rheumatology* (Oxford). 2018; 57(11): 2022-31. https://doi.org/10.1093/rheumatology/key202
35. WEVERS-DE BOER KV, HEIMANS L, VISSER K *et al*.: Determinants of reaching drug-free remission in patients with early rheumatoid or undifferentiated arthritis after one year of remission-steered treatment. *Rheumatology* (Oxford) 2015; 54(8): 1380-84. https://doi.org/10.1093/rheumatology/keu477
36. HASCHKA J, ENGLBRECHT M, HUEBER AJ *et al*.: Relapse rates in patients with rheumatoid arthritis in stable remission tapering or stopping antirheumatic therapy: interim results from the prospective randomised controlled RETRO study. *Ann Rheum Dis* 2016; 75(1): 45-51. https://doi.org/10.1136/annrheumdis-2014-206439
37. SCHETT G, EMERY P, TANAKA Y *et al*.: Tapering biologic and conventional DMARD therapy in rheumatoid arthritis: current evidence and future directions. *Ann Rheum Dis* 2016; 75(8): 1428-37. https://doi.org/10.1136/annrheumdis-2016-209201
38. DEKKERS JS, BERGSTRA SA, CHOPRA A *et al*.: Autoantibody status is not associated with early treatment response to first-line methotrexate in patients with early rheumatoid arthritis. *Rheumatology* (Oxford). 2019; 58(1): 149-53. https://doi.org/10.1093/rheumatology/key263
39. JONSSON MK, HENSVOLD AH, HANSSON M *et al*.: The role of anti-citrullinated protein antibody reactivities in an inception cohort of patients with rheumatoid arthritis receiving treat-to-target therapy. *Arthritis Res Ther* 2018; 20(1): 146. https://doi.org/10.1186/s13075-018-1635-7
40. MANEIRO RJ, SALGADO E, CARMONA L, GOMEZ-REINO JJ: Rheumatoid factor as predictor of response to abatacept, rituximab and tocilizumab in rheumatoid arthritis: systematic review and meta-analysis. *Semin Arthritis Rheum* 2013; 43(1): 9-17. https://doi.org/10.1016/j.semarthrit.2012.11.007
41. NÜSSLEIN HG, ALTEN R, GALEAZZI M *et al*.: Efficacy and prognostic factors of treatment retention with intravenous abatacept for rheumatoid arthritis: 24-month results from an international, prospective, real-world study. *Clin Exp Rheumatol* 2016; 34(3): 489-99.