In early arthritis patients, high HAQ at baseline and DAS28 at three months predict suboptimal outcomes at two years: a retrospective cohort study

A. Fanouriakis[1], I. Papalopoulos[1], I. Gergianaki[1], G. Spyrou[1], A. Erden[2], P. Rapsomaniki[1], M. Terizaki[1], N. Avgoustidis[1], A. Repa[1], N. Kougkas[1], G. Bertsias[1], D.T. Boumpas[3-5], P.I. Sidiropoulos[1]

[1]Department of Rheumatology, Clinical Immunology and Allergy, University Hospital of Heraklion, Greece; [2]Department of Rheumatology, Hacettepe University, Ankara, Turkey; [3]4th Department of Internal Medicine, Attikon University Hospital, Medical School, National and Kapodestrian University of Athens, Greece and Joint Academic Rheumatology Program, Medical School, National and Kapodestrian University of Athens, Greece; [4]Institute of Molecular Biology and Biotechnology, Foundation of Research and Technology-Hellas, Voutes, Heraklion, Greece; [5]Laboratory of Autoimmunity and Inflammation, Biomedical Research Foundation of the Academy of Athens, Greece.

Abstract

Objective

Early arthritis clinics (EAC) aim to improve rheumatoid arthritis (RA) outcomes by tailoring treatment targeting to remission. Our aim was to analyse disease course and relevant predictors over 2 years in early arthritis; we also assessed the applicability of the "treat-to-target approach" in a real-life EAC.

Methods

Patients with early arthritis recruited at the EAC of the University Hospital of Heraklion were followed prospectively according to a follow-up protocol for two years, without implementing a pre-specified treatment protocol, to capture real-life practices. Early predictors of "suboptimal outcomes" (high disease activity or HAQ>1.0 at 2 years) and biologic DMARD (bDMARD) initiation were evaluated with multivariate logistic regression. Intensification of treatment at 3 and 6 months and subsequent long-term outcome were also assessed.

Results

251 patients [RA (n=188), undifferentiated arthritis (n=63)] were included. Although both DAS28 and HAQ at 2 years improved significantly compared to baseline in RA patients [mean (SD) DAS28 and median (IQR) HAQ 3.70 (1.32) and 0.44 (0.75) at 2 years, p<0.001 for both compared to baseline], 43.7% still had moderate and 18.8% high disease activity. The most powerful predictor of suboptimal outcomes or bDMARD initiation in RA was high disease activity at three months (adjusted odds ratio 2.22 and 2.62, respectively). At three and six months 72.8% and 62.4% of patients with medium/high disease activity received treatment intensification, which resulted in significant decrease in disease activity at 2 years (p<0.001 for ΔDAS28).

Conclusion

DAS28 at three months was the most powerful predictor of suboptimal disease outcome during a 2-year follow-up in early RA. Despite significant DAS reductions, more than 50% of patients have active disease at two years. Failure to fully implement the treat-to-target strategy in our cohort could account for the low remission rates.

Key words

early arthritis, treatment, outcome, treat-to-target

*Antonis Fanouriakis, MD**
Ioannis Papalopoulos, MD
Irini Gergianaki, MD, PhD
Giorgis Spyrou, MD
Abdulsamet Erden, MD
Panagiota Rapsomaniki, BSc
Maria Terizaki, BSc
Nestor Avgoustidis, MD
Argyro Repa, MD
Nikolaos Kougkas, MD
George Bertsias, MD, PhD
Dimitrios T. Boumpas, MD, PhD, FACP
Prodromos I. Sidiropoulos, MD, PhD

**Current address: 4th Department of Internal Medicine, Attikon University Hospital, Medical School, National and Kapodestrian University of Athens, Greece.*

Please address correspondence and reprint requests to: Dr Antonis Fanouriakis, Rheumatology and Clinical Immunology, 4th Department of Internal Medicine, Attikon University Hospital, National and Kapodestrian University of Athens, 16345 Athens, Greece.
E-mail: afanour@med.uoa.gr

Received on August 21, 2017; accepted in revised form on January 22, 2018.

Competing interests: none declared.

Introduction

The course and natural history of rheumatoid arthritis (RA) varies widely and partly depends on timely diagnosis and adequate disease control at early stages. To this end, dedicated early arthritis clinics (EAC) have been established, in order to facilitate diagnosis and early initiation of disease-modifying antirheumatic drugs (DMARDs) (1).

The concept of "treat-to-target" (T2T) has been established as the treatment paradigm for RA in both clinical trials and routine clinical practice (1, 2). A therapeutic strategy based on tight control of disease activity aiming at remission has proven superior to usual care, in terms of better control of disease activity and less radiographic progression over time (3, 4). While it is beyond doubt that the lowest possible level of disease activity confers the best long-term outcome, the stringency of this approach raises doubts regarding its feasibility and actual implementation in everyday clinical care. Due to several physician- and patient-related reasons, true remissions may actually be rare in routine practice (5). A level of low or "low-moderate" disease activity is occasionally considered more "pragmatic" and acceptable by treating physicians, especially when coupled by normal functional status. Despite some recent reports (6), whether moderate or low-moderate disease activity in clinical practice is actually associated with increased disability in the long-term remains questionable.

The EAC of the Department of Rheumatology of the University Hospital of Heraklion is an inception cohort established in 2007, which follows patients with early inflammatory arthritis [RA or undifferentiated arthritis (UA)]. The objectives of the present analysis were to: i) assess outcome of early arthritis at 2 years, in terms of disease activity and function, ii) evaluate baseline and early prognostic factors for subsequent initiation of a biologic agent, presence of high disease activity and impaired function at 2 years and iii) examine the applicability and long-term outcome of a disease activity score based on 28 joints count (DAS28)-steered escalation of treatment early in the disease course.

Methods

Study design and population

This was a retrospective cohort study, from the Department of Rheumatology of the University Hospital of Heraklion, which serves as the referral center for 650,000 inhabitants of the island of Crete, Greece. Inclusion criteria for the EAC are: 1) patients with arthralgias or early arthritis (symptoms' duration <12 months) referred by the outpatient departments of the hospital or by primary care units of the region, 2) age >15 years and 3) absence of an alternative diagnosis (*e.g.* connective tissue disease, spondyloarthritis, fibromyalgia); such patients are not included in the EAC and are referred to other specialised clinics. Patients with crystal-induced arthritis are often diagnosed in the Emergency or Outpatient departments and thus are not typically referred to the EAC.

Patients with early RA (ACR/EULAR 2010 criteria (7)) or UA were followed quarterly for 2 years according to a follow-up protocol. Recruitment period was between 01/01/2007 and 01/07/2014, and patients were followed-up for 2 years. For those diagnosed prior to the publication of the 2010 RA criteria, application of the latter was feasible because all components of the criteria set (number of affected joints, RF/anti-CCP positivity, raised inflammatory markers and symptom duration) were documented during the first EAC visit. UA was defined as an early inflammatory oligo- or polyarthritis not fulfilling the ACR/EULAR 2010 criteria for RA (neither criteria for any other inflammatory arthritis), until the end of the follow-up period. According to the protocol, all patients had a prospective documentation of treatments received for inflammatory arthritis, laboratory results, disease activity and function measured by the DAS28 (8) and health assessment questionnaire (HAQ)(9) indices, respectively. For the purpose of this study, patients who had ≥2 visits in the EAC were included for the analysis (*i.e.* not all patients in the study completed 2 years follow-up).

Therapeutic decisions in the EAC were based on experienced physician judgment. Of note, the Clinic does not

follow a strict T2T protocol; rather, treatment modifications are based on a comprehensive assessment by a trained rheumatologist, following objective documentation of disease activity and function and taking into account patients' perspectives.

Outcome variables and T2T applicability

We investigated for baseline predictors of suboptimal outcomes during the following 2 years. As "suboptimal disease outcomes", we defined high disease activity (*i.e.* DAS28 >5.1) and impaired function (*i.e.* HAQ >1.0) at 2 years. We also sought for predictors of the use of biologic DMARDs (bDMARDs) at any time within the 2-year period.

In addition, we evaluated the applicability and outcome of the T2T paradigm. Specifically, patients with DAS28-defined moderate (MDA) or high (HDA) disease activity at 3 and 6 months of follow-up were assessed to document whether their therapy was intensified. Therapy intensification was defined as addition or dose escalation of one of the following synthetic disease-modifying drugs (sDMARDs): methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, or initiation of a biologic DMARD (bDMARD). Albeit glucocorticoids (GCs) are considered as disease-modifying drugs, addition of short-term glucocorticoid therapy was not considered as escalation of therapy for this study. In patients who were not offered treatment intensification as per the T2T paradigm, we also documented the reasons for this on a case-by-case basis. Reasons for no treatment intensification were categorised as follows: 1: Lack of provision of optimal treatment by the physician (no recommendation by physician without obvious reason); 2: Satisfactory overall patient condition, as per treating physician judgment (based on low HAQ and general impression); 3 Drug toxicity/intolerance or presence of comorbidities and 4: Recommended by physician, but patient unwillingness.

Statistical analysis

Data analyses were performed with IBM SPSS Statistics (v. 21.0, Chicago, Illinois, USA) and Stata 13 (StataCorp, College Station, TX, USA). Descriptive statistics were undertaken for continuous variables and mean values/standard deviation (SD) or median/interquartile range (IQR) were calculated, for normally and non-normally distributed variables, respectively (with only exception the number of tender and swollen joints, wherein range is provided to reflect the patient population more accurately). Chi-square or Fisher's exact test were used to compare categorical variables and student's t-test or non-parametric Mann-Whitney U-test were used to compare continuous variables, as appropriate. Binary logistic regression analysis was used to calculate the crude and adjusted odds ratios (OR) between various parameters and i) initiation of bDMARD at any time during follow-up, ii) presence of HDA (DAS28 >5.1) at 2 years and iii) HAQ >1.0 at 2 years. Potential predictors were selected based on previous studies and clinical relevance. Age, sex, symptom duration prior to diagnosis, disease activity (DAS28) and function (HAQ) at baseline and during the first 3 months of treatment, acute phase reactants (ESR, CRP), RF, anti-CCP status, were included in the regression model. Variables with a p-value <0.1 in univariate analysis were entered in the multivariate model and logistic regression with backward elimination was used for model reduction. Multicollinearity between independent variables was assessed with the calculation of the Condition Index and Variance Inflation Factors (VIFs). Among collinear variables, the variable with the strongest association at univariate level was selected for the multivariate model. For all comparisons, statistical significance was indicated as a two-sided p<0.05 and 95% confidence intervals (CI) were calculated.

The study was approved by the Institutional Review Board of the University Hospital of Heraklion, Crete (decision number: 1476/20-03-2012), and all patients provided written informed consent for their participation.

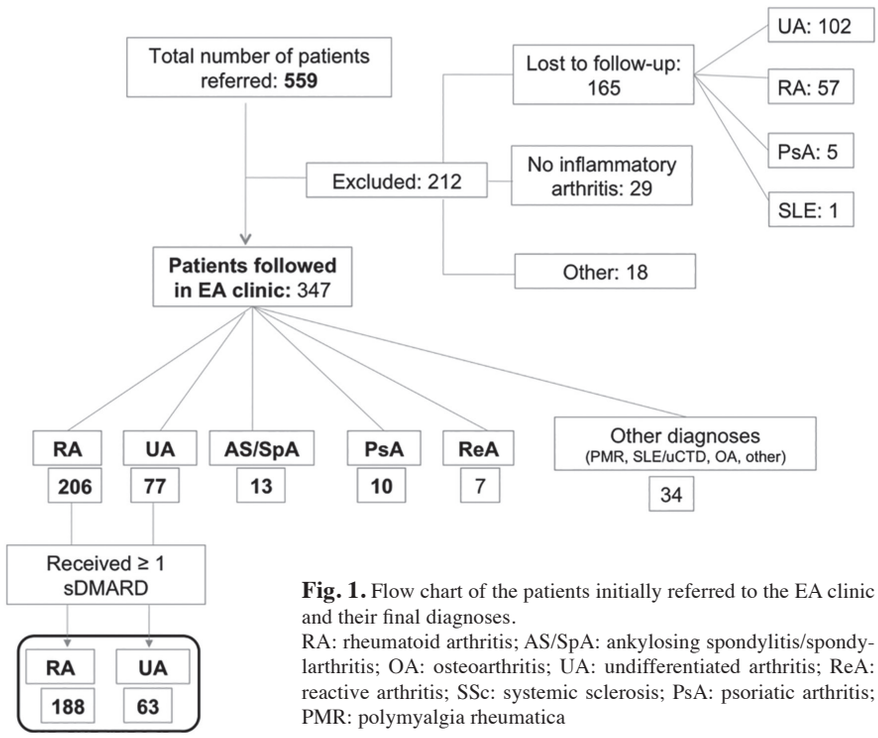

Fig. 1. Flow chart of the patients initially referred to the EA clinic and their final diagnoses.
RA: rheumatoid arthritis; AS/SpA: ankylosing spondylitis/spondylarthritis; OA: osteoarthritis; UA: undifferentiated arthritis; ReA: reactive arthritis; SSc: systemic sclerosis; PsA: psoriatic arthritis; PMR: polymyalgia rheumatica

Results

Baseline characteristics

From a total of 559 patients referred to the EAC, 283 patients had a final diagnosis of RA or UA (Fig. 1). During the course of follow-up, 251/283 (88.7%) patients received treatment with at least one sDMARD and were included in the analysis. The remaining 32 patients were either i) treated

with glucocorticoid monotherapy or ii) were lost-to-follow-up after 2 visits or iii) did not receive treatment based on personal preference.

Demographic and clinical characteristics of 251 patients at baseline are shown in Table I; 81.7% were women, the mean (SD) age at disease diagnosis was 54.9 (14.7) years, and 23.3% were positive for rheumatoid factor (RF) or/and anti-CCP antibodies. After 2 years of follow-up, 25.1% of the cohort still did not fulfill the ACR/EULAR criteria and thus, had a diagnosis of UA. At baseline, these patients were younger, had milder disease (joint counts, DAS28) and a better functional status (HAQ), compared to those with a final diagnosis of RA ($p<0.001$ for all comparisons, Table I).

Clinical assessment at baseline showed a moderate inflammatory burden of arthritis, especially in patients with RA. Specifically, the number [median (IQR)] of tender and swollen joints (28-joint count) was 6.0 (10.0) and 3.0 (7.0) respectively, while mean (SD) DAS28 was 4.61 (1.35). Of note, 37.2% of patients had high disease activity (DAS28 >5.1) and 21.9% reported a HAQ ≥1.

Disease evolution

Among patients with RA, at 3 and 6 months, 17.9% and 18.9% were in remission, while 8.3% and 11.9% were in low disease activity, respectively (*complete-case analysis*), indicating a high percentage of patients remaining in MDA/HDA at early disease stages (Fig. 2). After 2 years of follow-up, average DAS28 in the RA cohort was significantly reduced compared to baseline [n=80, mean (SD) 3.70 (1.32), $p<0.001$]; this improvement was evident from the first 3 months and maintained throughout all time points (Table II). However, 43.7% (35/80 of evaluable patients) still had MDA and 18.8% had HDA at 2 years, whereas 22.5% were in remission and 15.0% in low disease activity (LDA) (Fig. 2). We performed a sensitivity analysis to rule out the possibility that missing data have biased our results. Indeed, when RA patients with available data at 2 years (completers, n=80) were compared to non-completers (n=108) in several baseline characteristics, no differences were found (data not shown). Respective percentages for patients with UA were higher, with 54.5% and 76.9% of patients reaching LDA or remission at 18 and 24 months, respectively (total n=33 and 26, respectively, Table II).

Concerning functional improvement, a statistically significant decrease in HAQ was also observed as early as 3 months in patients with RA, and persisted over the whole follow-up period (Table II). The proportion of patients reporting a normal functional status (HAQ <0.25) increased gradually over

Table I. Demographic and clinical characteristics of patients with early rheumatoid or undifferentiated arthritis at baseline.

Characteristic	Total cohort (n=251)	RA (n=188)	UA (n=63)	*p*-value*
Age (years), mean (SD)	54.9 (14.7)	56.9 (13.4)	48.7 (16.6)	**<0.001**
Female gender, n (%)	205 (81.7)	156 (83.0)	49 (77.8)	0.97
Duration of symptoms (weeks), median (IQR)	24 (43)	24 (44)	48 (40)	0.10
DAS28, mean (SD)	4.61 (1.35)	4.80 (1.31)	4.05 (1.31)	**<0.001**
HAQ, median (IQR)	0.50 (0.70)	0.63 (0.88)	0.38 (0.62)	**<0.001**
Number of tender joints, median (range)	6.0 (1-28)	7.0 (1-28)	2.0 (1-20)	**<0.001**
Number of swollen joints, median (range)	3.0 (1-28)	4.0 (1-28)	2.0 (1-20)	**<0.001**
RF and/or anti-CCP (+), %	23.3	25.9	15.6	0.06
ESR (mm/hr), median (IQR)	20.0 (23.0)	20.5 (22.5)	20.0 (27.0)	0.84
CRP (mg/dl), median (IQR)	0.4 (0.7)	0.4 (0.8)	0.3 (0.2)	0.91
Patient VAS global, mean (SD)	5.4 (2.6)	5.5 (2.6)	5.1 (2.6)	0.12

*For the comparison between RA and UA patients.
RA: rheumatoid arthritis; UA: undifferentiated arthritis.

Table II. Kinetics of DAS28, of HAQ and of % of patients with normal function (HAQ <0.25) over time in early rheumatoid arthritis and undifferentiated arthritis.

	Rheumatoid arthritis			Undifferentiated arthritis		
	Mean (SD) DAS28		*p*-value (compared to baseline)	Mean (SD) DAS28		*p*-value (compared to baseline)
Baseline	n=188	4.80 (1.31)	NA	n=63	4.05 (1.31)	NA
3 months	n=156	4.08 (1.31)	**<0.001**	n=57	3.25 (1.21)	**<0.001**
6 months	n=159	3.96 (1.37)	**<0.001**	n=46	3.08 (1.25)	**<0.001**
9 months	n=135	3.88 (1.39)	**<0.001**	n=42	2.91 (1.08)	**<0.001**
12 months	n=130	3.83 (1.30)	**<0.001**	n=41	3.06 (1.25)	**<0.001**
18 months	n=116	3.70 (1.29)	**<0.001**	n=33	2.92 (1.09)	**<0.001**
24 months	n=80	3.70 (1.32)	**<0.001**	n=26	2.61 (1.12)	**<0.001**
	Median (IQR) HAQ		*p*-value (compared to baseline)	Median (IQR) HAQ		*p*-value (compared to baseline)
Baseline	n=151	0.63 (0.88)	NA	n=55	0.38 (0.62)	NA
3 months	n=146	0.50 (0.87)	**0.016**	n=55	0.25 (0.50)	0.49
6 months	n=138	0.50 (0.87)	**0.048**	n=42	0.25 (0.50)	0.10
9 months	n=121	0.50 (1.0)	0.13	n=44	0.19 (0.44)	**0.035**
12 months	n=123	0.38 (0.75)	0.11	n=38	0.28 (0.63)	0.20
18 months	n=113	0.38 (0.62)	**0.008**	n=34	0.25 (0.63)	0.34
24 months	n=98	0.44 (0.75)	**0.021**	n=28	0.13 (0.50)	**0.007**
	HAQ <0.25, n (%)			HAQ <0.25, n (%)		
Baseline	n=151	33 (21.8)		n=55	17 (30.9)	
3 months	n=146	39 (26.7)		n=55	24 (43.6)	
6 months	n=138	44 (31.9)		n=42	19 (45.2)	
9 months	n=121	44 (36.4)		n=44	22 (50.0)	
12 months	n=123	39 (31.7)		n=38	14 (36.8)	
18 months	n=113	39 (34.5)		n=34	15 (44.1)	
24 months	n=98	29 (29.6)		n=28	16 (57.1)	

Table III. Association of parameters at baseline and early during the course of the disease with DAS28>5.1, HAQ>1 at 24 months, and subsequent initiation of a biologic agent in early rheumatoid arthritis.

Variable	DAS28 >5.1 at 2 years		HAQ >1 at 2 years		Start of biologic DMARD	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Duration of symptoms (weeks)	1.00 (1.00-1.01)		1.06 (1.00-1.01)	1.00 (1.00-1.01)	1.00 (1.00-1.01)	1.00 (1.00-1.01)
Baseline DAS28	2.13 (1.18-3.86)		1.19 (0.82-1.72)		1.30 (0.95-1.76)	
Baseline HAQ	4.85 (1.31-17.99)	2.85 (0.69-11.76)	11.27 (3.24-39.18)	**12.63 (2.67-59.78)**	2.25 (1.09-4.65)	2.12 (0.77-5.80)
Baseline CRP	0.66 (0.29-1.52)		0.67 (0.37-1.21)		0.78 (0.55-1.11)	
Baseline ESR	0.99 (0.97-1.02)		0.98 (0.95-1.01)		0.98 (0.95-1.00)	**0.95 (0.90-0.99)**
RF (+)	3.33 (0.67-16.47)		1.21 (0.22-6.57)		2.45 (0.84-7.10)	3.71 (0.70-19.82)
Anti-CCP (+)	0.87 (0.16-4.61)		0.25 (0.03-2.08)		1.85 (0.65-5.23)	
DAS28 at 3 months	2.41 (1.23-4.74)	**2.62 (1.20-5.72)**	2.26 (1.33-3.82)	**2.31 (1.14-4.71)**	2.10 (1.41-3.13)	**2.22 (1.36-3.62)**
HAQ at 3 months	3.72 (1.15-11.97)		3.90 (1.45-10.49)		1.95 (1.01-3.78)	

Multivariate association of risk factors for any of the three "suboptimal outcome measures". Age, sex, symptom duration prior to diagnosis, disease activity (DAS28) and function (HAQ) at baseline and during the first 3 months of treatment, acute phase reactants (ESR, CRP), RF, anti-CCP status, were included in the univariate regression model. All factors found to be significantly associated in the univariate models (at a level $p<0.1$) were then inserted into the final multivariate model. Regarding DAS and HAQ, only one time point was inserted in the final model (3 months and baseline, respectively, owing to the stronger association at univariate level) to avoid collinearity.

time, reaching between 30–40% of patients from month 6 onwards (Table II). However, at 12 and 24 months, 24.4% and 22.4% of evaluable patients still reported a HAQ >1.0, respectively.

Predictors of bDMARD initiation and suboptimal disease outcomes at 2 years

Over the course of follow-up, 16.5% (n=31) of RA and 6.4% (n=4) of UA patients were started on a bDMARD. Patients with UA were not analysed further due to the relatively small sample size. For RA patients, the mean time (SD) of bDMARD initiation was 10.4 (6.2) months after first evaluation in the EAC, while DAS28 at the time of bDMARD start was 5.05 (1.02). At baseline, RA patients who subsequently started a bDMARD had a higher median HAQ compared to patients who did not (0.88 *vs*. 0.50, respectively, $p=0.026$). No other differences in baseline characteristics reached statistical significance, although bDMARD-treated patients tended to have more swollen and tender joints (data not shown).

We analysed baseline and early predictors of bDMARD initiation (Table III, complete-case analysis). In multivariate analysis, DAS28 at 3 months was the only significant predictor thereof [adjusted OR (95% CI) 2.22 (1.36–3.62]. We also sought for independent predictors of disease evolution (DAS28>5.1 and HAQ >1) during the first 2 years (see Methods). Regarding high disease activity at 2 years, multivariate analysis showed that again only DAS28 at 3 months predicted a DAS28 >5.1 at 2 years [adjusted OR (95% CI) 2.62 (1.20–5.72), Table III]. Concerning functional impairment, high baseline HAQ showed a strong independent association with a HAQ >1.0 at 2 years [12.63 (2.67–59.78)], along with DAS28 at 3 months [2.31 (1.14–4.71)] similar to previous associations. Interestingly, when the whole cohort of RA and UA patients (n=251) were analysed as a group, no significant changes in the above predictors were found (data not shown).

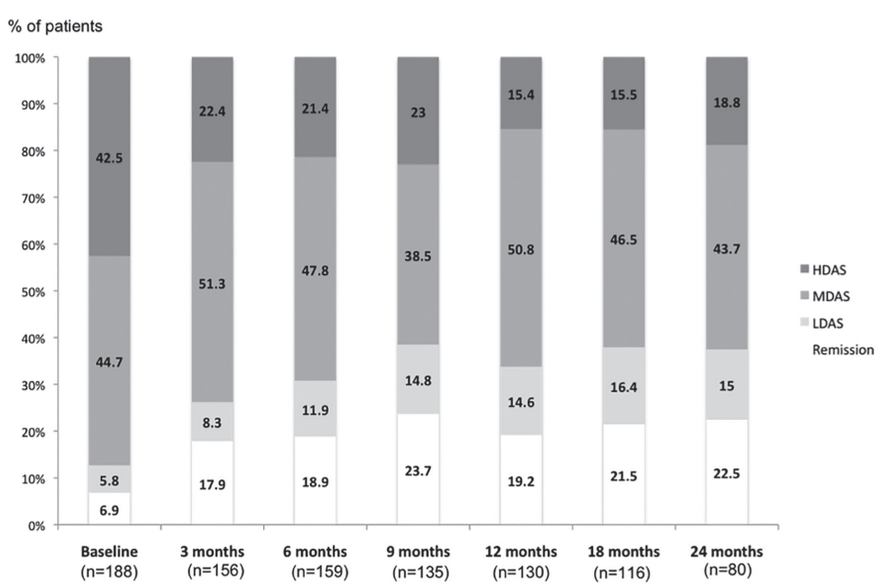

Fig. 2. Levels of disease activity, according to DAS28, over 2 years of follow-up in patients with early rheumatoid arthritis (complete-case analysis).
HDAS: high disease activity state (DAS28 >5.1); MDAS: medium disease activity state (3.2 <DAS28 <5.1); LDAS: low disease activity state (2.6 <DAS28 <3.2).

Long-term effects of treatment intensification at early disease stages

We aimed to assess the applicability and clinical outcome of treatment intensification based on disease activity status in patients with RA. We particularly focused on treatment escalation in patients with MDA or HDA at 3 and 6

months after first evaluation in the EAC (critical time points in early RA). At 3 months, 72.8% (83/114) of RA patients with MDA or HDA had their treatment escalated (as defined in *Methods*), while at 6 months, a lower percentage (62.4%, 68/109) received treatment intensification. Disease outcome was assessed longitudinally until 2 years after baseline (Fig. 3). DAS28 reductions were greater in patients who received treatment intensification at 3 months compared to patients who did not (mean ΔDAS28 at 12 and 24 months -0.62 and -0.83 *vs*. -0.20 and + 0.15, respectively (Fig. 3a). Interestingly, ΔDAS was comparable at 24 months between the group with treatment escalation and that with no treatment escalation at 6 months time-point (Fig. 3b).

We next explored the reasons for a lack of recommendation for T2T by the treating physicians. Most common reason for non-provision of treatment escalation at 3 months was a satisfactory overall condition/low HAQ (16/31 patients, 51.6%) followed by no recommendation by physician without obvious reason (10/31, 32.5%), indicative of a mainly physician-driven decision. Respective reasons at the 6-month time point were more homogeneously distributed between physician- and patient-related reasons (12, 11, 9, and 9 patients for overall satisfactory status, no reason, patient unwillingness and drug intolerance/comorbidities, respectively). Nevertheless, provision or not of optimal treatment for any reason (physician- *vs*. patient-related reasons) was not associated with adverse outcomes at 2 years (HAQ >1.0 or HDA) (data not shown).

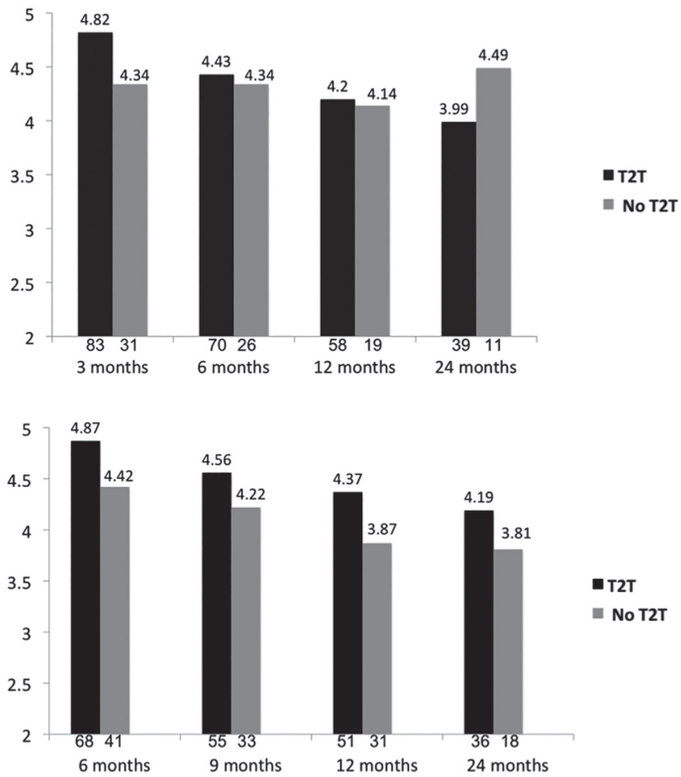

Fig. 3. Kinetics of DAS28 for RA patients with moderate or high disease activity at 3 months (top graph) and 6 months (bottom graph) after first evaluation at the EAC, according to therapy intensification (T2T) or not. Numbers beneath each column indicate the number of patients with available data in each group and time point.

Discussion

Incorporating recent evidence, the recommendations for the management of both RA and EA have set the achievement of clinical remission as the optimal treatment target (10, 11). In the context of early disease, EAC provide a framework for earlier initiation of treatment and more stringent patient monitoring. In the present analysis from the EAC of the Department of Rheumatology, University of Crete, we found that 74.9% of patients had a diagnosis of RA and they had a more active disease, compared to UA patients. Initial DMARD treatment in early RA induced remission or LDA in 18.9% and 11.9% respectively at 6 months (in UA, the cumulative percentage of remission/LDA almost reached 50%). Thereafter, the group of MDA and HDA who received treatment intensification had a further significant improvement in DAS28 at both 12 and 24 months. Nevertheless, remission was achieved by hardly over 20% of patients. Analysis for predictors of different "disease suboptimal outcomes" during 2 years showed that baseline functional status and disease activity at 3 months were the most important factors.

Data from EAC have provided valuable information regarding differential diagnosis, prognosis and evolution of early inflammatory arthritis. In our cohort with a follow-up of 2 years, after excluding patients with spondyloarthropathies and other rheumatic diseases, 74.9% had a diagnosis of RA and 25.1% had UA. Patients with UA had a milder disease and better functional status at baseline. Our data are comparable with data from other EAC concerning diagnosis and inflammatory burden of arthritis, both in older and more recent studies (12-14).

The main goal of early diagnosis and treatment of inflammatory arthritis is control of inflammation in order to achieve better long-term outcomes. In our cohort, 13.9% of patients started a bDMARD during the 2-year period. At 3 months of treatment, 17.9% of RA patients had achieved a DAS28 remission status, while 8.3% were in LDA. The proportion of patients in remission was rather constant during follow-up (19.2% and 22.5% at 12 and 24 months), while that of LDA increased to 14.6% and 15.0%, respectively. These data are lower compared to those reported from randomised studies of early RA based on tight-control clinical protocols (DREAM, CAMERA), where DAS28 remission rates are achieved by 50%-55% of patients (2, 15), or observational studies implementing T2T protocols (16). Instead, our data are more comparable to those from observational studies originating from similar EAC; Gremese *at al*. analysed combined data from 3 EAC, and reported a 34.3% DAS28 remission rate at 12 months (12), while earlier data from the ERAS cohort reported DAS remission rates of

25% at 3 years (17). Factors accounting for lower remissions rates in our cohort could be delayed diagnosis and treatment initiation, since median symptom duration at enrollment was 24 weeks (Table I). Multiple studies have shown that initiation of DMARDs within the first 12 weeks is a common denominator for better clinical and radiological outcomes (12, 18, 19). Moreover, only 13.9% of our patients started bDMARD, which is lower compared to that reported by other observational studies of early RA (31.6% in the study of Gremese *et al*. (9)), a factor possibly contributing to lower remission rates (20).

We also analysed applicability and outcome of treatment intensification for the group of patients with MDA and HDA at 3 and 6 months, time points where treatment decisions according to disease activity are usually taken. We found that a step-up in treatment was done in 62–74% of RA patients not achieving remission or LDA at 3-6 months. As described in Methods, patients were not treated based on a strict T2T protocol. Nevertheless, modifications of treatment were based on a comprehensive clinical assessment by a trained rheumatologist, also taking into account the patients' perspective. Long-term outcomes of treatment intensification were assessed and, in the group of MDA/HDA who received treatment intensification, a further improvement in DAS28 at month 12 and 24 was noted (at 24 months ΔDAS -0.83 and -0.68 for both 3- and 6-months). Deviations from the T2T approach in clinical practice have been described. Wabe *et al*. recently reported "treatment protocol deviations" in 24.5% of patients, in a retrospective cohort study of early RA; continuation of existing treatment rather than intensifying therapy according to T2T approach, was the most common type of deviation (59.9%) (21). Interestingly, even in the context of a randomised clinical trial (DREAM study), where treatment was guided by a strict T2T protocol, in 34.9% of patients not in remission treatment was not intensified (2). Reasons for not following a T2T approach are both physician- and patient-related. Comorbidities, drug toxicity and safety concerns, patient-driven preferences, non-inflammatory musculoskeletal pain and insufficient time to assess the effect of recently initiated DMARDs have been reported (22). Indeed, in our study we also found that a decision not to offer treatment intensification was influenced by both physician and patient-related reasons, without a clear trend for one over the other. Interestingly, in both the 2013 and 2016 updated EULAR recommendations for the management of RA, it is clearly stated that treatment decisions are based on disease activity and other patient factors, such as progression of structural damage, comorbidities and safety issues (11, 23).

We finally assessed for early disease predictors for initiation of a bDMARD as well as for "suboptimal" outcomes during the follow-up period. Between several baseline and early disease course characteristics, high DAS28 at 3 months was the common independent predictor for all 3 outcomes. Interestingly, functional impairment at baseline strongly predicted a worse functional status at 2 years (OR 12.6). All the above characteristics have been associated with various short- or long-term outcomes in several studies of early RA or early UA, both before and after more stringent approaches for disease control were introduced (12, 16-19, 24). Interestingly, and for the first time in an EA cohort, disease activity at 3 months was found to predict several adverse outcomes. This underlines the clinical significance of rapid control of inflammatory status as early as possible, in order to improve outcomes and preserve patient function (25).

The main limitation of our study relates to the presence of missing data (complete-case analysis was performed in all parts of the study). We decided not to apply last-observation-carried-forward or multiple imputation methods, because they could introduce more bias in the case of our study than complete-case analysis (26, 27). Additional limitations that need acknowledgement are the lack of a radiological outcome at 2 years and non-application of a strict treatment clinical protocol, all common drawbacks of observational studies. Finally, the number of patients with UA was relatively small to carry out all analyses, comparatively to RA. We did not calculate sample size or power, because our study was not designed to address and test a particular hypothesis or difference between treatment arms; rather, it attempted to capture real-life practices in an early arthritis cohort of a tertiary centre. In this regard, calculation of sample size did not pertain to our work. These caveats notwithstanding, long-term data from a real-life setting constitute an important source of information, in order to better understand the limitations of current practice.

In conclusion, in this analysis from an EA cohort of a real-world academic setting, we found that a little more than 20% of early RA patients achieve remission and 15.0% LDA at 2 years. The major predictor of adverse disease evolution was disease activity status at 3 months, an easy to use tool in clinical practice, once more underlying the importance of early disease control to achieve better outcomes. Earlier referral and increase of T2T implementation in real-life should be pursued in order to improve early arthritis outcomes in clinical practice.

Acknowledgments

The authors would like to thank Irini Flouri, MD, for her critical review of the manuscript and thoughtful comments.

References

1. GOEKOOP-RUITERMAN YP, DE VRIES-BOUWSTRA JK, ALLAART CF *et al*.: Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2007; 146: 406-15.
2. SCHIPPER LG, VERMEER M, KUPER HH *et al*.: A tight control treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: a study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring registry. *Ann Rheum Dis* 2012; 71: 845-50.
3. GRIGOR C, CAPELL H, STIRLING A *et al*.: Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 2004; 364: 263-9.
4. BALDUZZI S, SCIRE CA, SAKELLARIOU G *et al*.: In early inflammatory polyarthritis more intensive management according to the 2010 ACR/EULAR criteria leads to higher rates of clinical remission: comparison of two cohorts treated according to different treat-to-target pro-

tocols. *Clin Exp Rheumatol* 2017; 35: 401-5.
5. ACEBES C, ANDREU JL, BALSA A *et al*.: Exploring the remission concept in rheumatoid arthritis with patients and rheumatologists: time for a new approach? *Clin Exp Rheumatol* 2017; 35: 816-22.
6. NIKIPHOROU E, NORTON S, YOUNG A *et al*.: Association between rheumatoid arthritis disease activity, progression of functional limitation and long-term risk of orthopaedic surgery: combined analysis of two prospective cohorts supports EULAR treat to target DAS thresholds. *Ann Rheum Dis* 2016; 75: 2080-6.
7. ALETAHA D, NEOGI T, SILMAN AJ *et al*.: 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010; 69: 1580-8.
8. PREVOO ML, VAN 'T HOF MA, KUPER HH, VAN LEEUWEN MA, VAN DE PUTTE LB, VAN RIEL PL: Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 44-8.
9. PINCUS T, SUMMEY JA, SORACI SA, JR., WALLSTON KA, HUMMON NP: Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. *Arthritis Rheum* 1983; 26: 1346-53.
10. COMBE B, LANDEWE R, DAIEN CI *et al*.: 2016 update of the EULAR recommendations for the management of early arthritis. *Ann Rheum Dis* 2017; 76: 948-59.
11. SMOLEN JS, LANDEWE R, BIJLSMA J *et al*.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis* 2017; 76: 960-77.
12. GREMESE E, SALAFFI F, BOSELLO SL *et al*.: Very early rheumatoid arthritis as a predictor of remission: a multicentre real life prospective study. *Ann Rheum Dis* 2013; 72: 858-62.
13. HUA C, DAIEN CI, COMBE B, LANDEWÉ R: Diagnosis, prognosis and classification of early arthritis: results of a systematic review informing the 2016 update of the EULAR recommendations for the management of early arthritis. *RMD Open* 2017; 3: e000406.
14. JANSEN LM, VAN SCHAARDENBURG D, VAN DER HORST-BRUINSMA IE, DIJKMANS BA: One year outcome of undifferentiated polyarthritis. *Ann Rheum Dis* 2002; 61: 700-3.
15. VERSTAPPEN SM, JACOBS JW, VAN DER VEEN MJ *et al*.: Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). *Ann Rheum Dis* 2007; 66: 1443-9.
16. HORTON SC, TAN AL, FREESTON JE, WAKEFIELD RJ, BUCH MH, EMERY P: Discordance between the predictors of clinical and imaging remission in patients with early rheumatoid arthritis in clinical practice: implications for the use of ultrasound within a treatment-to-target strategy. *Rheumatology* (Oxford) 2016; 55: 1177-87.
17. JAYAKUMAR K, NORTON S, DIXEY J *et al*.: Sustained clinical remission in rheumatoid arthritis: prevalence and prognostic factors in an inception cohort of patients treated with conventional DMARDS. *Rheumatology* (Oxford) 2012; 51: 169-75.
18. LUKAS C, COMBE B, RAVAUD P, SIBILIA J, LANDEWÉ R, VAN DER HEIJDE D: Favorable effect of very early disease-modifying antirheumatic drug treatment on radiographic progression in early inflammatory arthritis: Data from the Etude et Suivi des polyarthrites indifferenciees recentes (study and followup of early undifferentiated polyarthritis). *Arthritis Rheum* 2011; 63: 1804-11.
19. VAN DER WOUDE D, YOUNG A, JAYAKUMAR K *et al*.: Prevalence of and predictive factors for sustained disease-modifying antirheumatic drug-free remission in rheumatoid arthritis: results from two large early arthritis cohorts. *Arthritis Rheum* 2009; 60: 2262-71.
20. LAMPROPOULOS CE, ORFANOS P, MANOUSSAKIS MN, TZIOUFAS AG, MOUTSOPOULOS HM, VLACHOYIANNOPOULOS PG: Treat-to-target biologic therapy in patients with rheumatoid arthritis is more efficacious and safe compared to delayed initiation of biologics: a real-world study. *Clin Exp Rheumatol* 2017; 35: 192-200.
21. WABE N, SORICH MJ, WECHALEKAR MD *et al*.: Characterising deviation from treat-to-target strategies for early rheumatoid arthritis: the first three years. *Arthritis Res Ther* 2015; 17: 48.
22. TYMMS K, ZOCHLING J, SCOTT J *et al*.: Barriers to optimal disease control for rheumatoid arthritis patients with moderate and high disease activity. *Arthritis Care Res* (Hoboken) 2014; 66: 190-6.
23. SMOLEN JS, LANDEWÉ R, BREEDVELD FC *et al*.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014; 73: 492-509.
24. KAWASHIRI SY, NISHINO A, SUZUKI T *et al*.: Rapid improvement of Clinical Disease Activity Index (CDAI) at 3 months predicts a preferable CDAI outcome at 1 year in active rheumatoid arthritis patients treated with tocilizumab: results from an observational investigation of daily clinical practice. *Clin Exp Rheumatol* 2016; 34: 808-12.
25. LEVITSKY A, WICK MC, MOTTONEN T *et al*.: Early treatment intensification induces favourable radiographic outcomes according to predicted versus observed radiographic progression in early rheumatoid arthritis: a subanalysis of the randomised FIN-RACo and NEO-RACo trials. *Clin Exp Rheumatol* 2016; 34: 1065-71.
26. LACHIN JM: Fallacies of last observation carried forward analyses. *Clin Trials* 2016; 13: 161-8.
27. LEE KJ, SIMPSON JA: Introduction to multiple imputation for dealing with missing data. *Respirology* 2014; 19: 162-7.