




Treatment patterns and achievement of the treat-to-target goals in a real-life rheumatoid arthritis patient cohort: data from 1317 patients

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Abstract

Background: Data regarding the real-life predictors of low disease activity (LDA) in rheumatoid arthritis (RA) patients are limited. Our aim was to evaluate the rate and predictors of LDA and treatment patterns in RA.

Methods: This was a multicenter, prospective, RA cohort study where patients were evaluated in two different time points approximately 12 months apart. Statistical analysis was performed in order to identify predictors of LDA while patterns of disease-modifying anti-rheumatic drug [DMARDs; conventional synthetic (csDMARD) or biologic (bDMARD)] and glucocorticoid (GC) use were also recorded.

Results: The total number of patients included was 1317 (79% females, mean age: 62.9 years, mean disease duration: 10.3 years). After 1 year, 57% had achieved LDA (DAS28ESR < 3.2) while 43% did not (34%: moderate disease activity: DAS28ESR ≥ 3.2 to < 5.1, 9%: high disease activity, DAS28ESR ≥ 5.1). By multivariate analysis, male sex was positively associated with LDA [odds ratio (OR) = 2.29 $p < 0.001$] whereas advanced age (OR = 0.98, $p = 0.005$), high Health Assessment Questionnaire (HAQ) score (OR = 0.57, $p < 0.001$), use of GCs (OR = 0.75, $p = 0.037$) or ≥ 2 bDMARDs (OR = 0.61, $p = 0.002$), high co-morbidity index (OR = 0.86, $p = 0.011$) and obesity (OR = 0.62, $p = 0.002$) were negative predictors of LDA. During follow-up, among active patients (DAS28ESR > 3.2), 21% initiated (among csDMARDs users) and 22% switched (among bDMARDs users) their bDMARDs.

Conclusion: In a real-life RA cohort, during 1 year of follow-up, 43% of patients do not reach treatment targets while only ~20% of those with active RA started or switched their bDMARDs. Male sex, younger age, lower HAQ, body mass index and co-morbidity index were independent factors associated with LDA while use of GCs or ≥ 2 bDMARDs were negative predictors.

Keywords: biologic therapy, co-morbidities, disease activity, rheumatoid arthritis

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Introduction

The advances in the therapeutic landscape of rheumatoid arthritis (RA) have substantially improved the quality of life of patients living with the disease, as the introduction of biologic disease-modifying anti-rheumatic drugs (bDMARDs) has resulted in slower disease progression, less chronic irreversible damage, higher functional capacity, lower rates of arthroplasties and even lower risk for extra-articular complications, such as cardiovascular events.¹ These favorable outcomes could be attributed to a number of factors,² including earlier diagnosis, improved treatment strategies [implementation of the treat-to-target (T2T) approach],³ more aggressive management of comorbidities⁴ and obviously the introduction of newer therapies such as the bDMARDs and oral targeted synthetic DMARDs (tsDMARDs).

However, despite all these advances, a substantial proportion of RA patients fail to achieve or to remain in remission/low disease activity (LDA).⁵ Real world data from registries have identified several factors associated with remission after treatment initiation in patients with early RA,^{6,7} albeit predictors of inadequate responses are ill-recognized in patients with longstanding disease.

Although the European League against Rheumatism (EULAR) Recommendations and the American College of Rheumatology (ACR) Guidelines for the management of RA suggest a T2T strategy consisting of adjusting therapy (initiating or switching DMARD therapies) if no improvement is observed in 3 months or target activity is not achieved in 6 months,^{3,8,9} the extent and success of the adoption of this approach in daily clinical practice has not been yet fully elucidated. Furthermore, for patients with moderate disease activity (MDA; DAS28ESR = 3.2–5.1), who currently constitute the most common RA patient subset in clinical practice, such real-life, longitudinal data are limited.^{10–12}

In this study, we prospectively evaluated the rate and predictors of achievement of LDA/remission in a large, real-life, multicenter RA cohort with a special focus in the subgroup of patients with MDA.

Materials and methods

Patients and study design

We conducted a multicenter, prospective study under the auspices of the RA Study Group of

the Greek Rheumatology Society as recently reported.¹³ Among the participating centers were academic and non-academic rheumatology departments, National Health System outpatient clinics and private offices. Inclusion criteria included age ≥ 18 years and RA diagnosis according to the ACR/EULAR criteria.¹⁴ Ethical approval was provided by the Joint Rheumatology Program (Hippokratation General Hospital as the co-ordinating center, 64/16-4-2015 and 7/23-3-2016) as well as by the local institutional boards of participating centers. Informed consent was provided by all patients at first evaluation.

According to the protocol, the study was divided into three successive phases. During phase I, an initial cross-section of RA patients was performed (first evaluation, June 2015–September 2016). Collected data were entered either through a printed case-reporting form or *via* a web-based form (www.rheumstudygrps.gr). The results of phase I have been published recently.¹³

During phase I, the following data were collected:

- *Patient and disease characteristics:* age, sex, weight, height, disease duration, working status, educational status, smoking and alcohol habits, disease activity assessed by the DAS28 (Disease Activity Score using 28 joints) erythrocyte sedimentation rate (ESR) score, functional status assessed by the Health Assessment Questionnaire (HAQ), serological status [presence or absence of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP)], presence of erosions in plain joint X-rays (physician reported), history of joint arthroplasties and RA-related interstitial lung disease. According to their disease duration, patients were further classified to those with “early” (≤ 2 years) or “long-standing” (> 2 years) disease.
- *Treatment patterns:* for each patient, past and current use of anti-rheumatic medications (including current dose and reasons for previous discontinuation) was also recorded. Anti-rheumatic medications included non-steroidal anti-inflammatory drugs, analgesics, glucocorticoids (GCs) and DMARDs, either conventional synthetic (cs)DMARDs or bDMARDs.
- *Comorbidities:* hyperlipidemia (use of lipid-lowering therapy), coronary artery disease

(treatment and/or history of stable angina, acute coronary syndrome or angioplasty/coronary artery bypass surgery), cerebrovascular disease (treatment and/or history of thrombotic or hemorrhagic stroke), peripheral vascular disease (specific treatment and/or history of revascularization), diabetes mellitus (use of antidiabetic agents and/or insulin), chronic obstructive pulmonary disease (with or without use of oxygen therapy at home), arterial hypertension (use of anti-hypertensive medications), depression (use of anti-depressives), osteoporosis (use of anti-osteoporotic therapies and/or history of osteoporotic fractures), current or past hepatitis B virus (HBV) infection (documented by the specific serology including HBsAg, anti-HBc and anti-HBs antibodies), current or past hepatitis C virus (HCV) infection (documented by anti-HCV antibodies and HCV-RNA testing), history of tuberculosis (TB) or latent TB infection, documented by a positive tuberculin skin test or an interferon-gamma release assay, history of herpes zoster, current or past history of neoplastic diseases and history of vaccination against influenza (in the last year or in the past), *Streptococcus pneumoniae* and HBV, history of hospitalization during the last 12 months and history of serious infection. Rheumatic disease comorbidity index (RDCI) was used as a composite co-morbidity score.¹⁵

During phase II (June 2016–September 2017), patients from the initial cohort were prospectively re-evaluated approximately 12 months after their first evaluation and a new set of data was collected with the same methods as phase I (printed or web-based forms).

These included:

- *Disease characteristics* (DAS28ESR, HAQ);
- *Serious events between the two evaluations* (serious infections requiring hospitalization, arthroplasties, cardiovascular events, hospitalization for any reason, osteoporotic fractures, neoplasias);
- *Treatment changes* (discontinuation and current treatment).

In the current study, we included RA patients who had available DAS28ESR at both time points (first evaluation visit during phase I and 2nd

evaluation during phase II approximately 1 year later). Patients' disease activity was categorized as low (LDA, <3.2), medium (MDA, ≥ 3.2 to <5.1) and high (HDA, ≥ 5.1) according to the DAS28ESR score. Furthermore, patients with MDA ($n=493$, DAS28ESR = 3.2–5.1) were further categorized into those with "lower" (DAS28ESR: 3.2–4.1, $n=199$, 40.4%) or "higher" (DAS28ESR: 4.2–5.1 $n=294$, 59.6%) disease activity at first evaluation.

Statistical analysis

All statistical analyses were performed with SPSS (IBM SPSS Statistics for Windows, v. 20.0., IBM Corp., Armonk, NY, USA) and STATA 13 (StataCorp) software. Demographic and descriptive continuous variables with normal distribution are expressed as mean (SD), whereas non-normally distributed data are presented as median values (interquartile range). Categorical variables are expressed as percentages. Chi square or Fisher's exact test was used for comparison of dichotomous and Mann–Whitney, *t*-test or one-way analysis of variance for continuous variables. Related samples were compared with Wilcoxon and McNemar's tests. Threshold of statistical significance was defined as a *p*-value < 0.05 . Among patients with MDA or HDA, univariate and multivariate logistic regression analysis was implemented in order to identify factors associated with changes in disease activity and initiation or switch in treatment type. Variables with *p*-value < 0.2 were included in the multivariate model. Variables with *p*-value < 0.1 , as well as those of biological significance (sex and age), were retained until the final stage of multivariate analysis (backward selection). Outcomes of logistic regression analysis are displayed as odds ratios (ORs) and their respective 95% confidence intervals (CIs).

Results

Patient characteristics at first evaluation

Among 2491 patients evaluated initially as reported in details in our previous publication,¹³ 1549 (62.2%) were available for a second evaluation after a median period of 13 months. With the exception of the more frequent use of bDMARDs (45% *versus* 35%) and dyslipidemia (35% *versus* 30%) and less frequent use of GCs (37% *versus* 45%), no other significant differences were noted between those with both evaluations ($n=1549$)

and those with only the first evaluation available, respectively ($n=942$; see Supplemental Material Table 1 online). A total of 1317 patients (85%) with available complete DAS28ESR data were included in the current study. With the exception of lower HAQ and higher csDMARD use at first evaluation, there were no other statistically significant differences between those included ($n=1317$) and not included ($n=232$), respectively in the analysis (Supplemental Table 2).

The characteristics of the 1317 patients are shown in Table 1; most patients were women (79%) with a mean age of 62.9 years and long disease duration (mean: 10.3 years). Almost half (54%) were RF and/or anti-CCP+, 44% had erosive disease while 9% had had an arthroplasty in the past. Regarding disease activity, the mean DAS28ESR was 3.36 and the median HAQ 0.48. Co-morbidities were common (63%; 825/1317) including hypertension (43%), dyslipidemia (34%), osteoporosis (28%) and diabetes mellitus (13%). Approximately one-third of patients (34%) had ≥ 2 co-morbidities (see Supplemental Figure 1) while one out four patients was obese [body mass index (BMI) >30 kg/m²; 24.6%; Table 1].

In terms of treatment patterns (Table 1), 85% were on csDMARDs (50% as monotherapy and 35% in combination with bDMARDs) and 46% on bDMARDs (11% as monotherapy and 35% in combination with csDMARDs). Among bDMARD-treated patients, almost half had been already exposed to >1 bDMARD (49%). Approximately one-third of patients (36%) were on GCs (mean daily prednisolone dose: 4.7 mg).

Attainment of LDA during follow-up

At first evaluation 52% of patients were on LDA, 37% on MDA and 11% on HDA; at re-evaluation 1 year later, the respective rates were 57% (+5%), 34% (-3%) and 9% (-2%, $p<0.001$; Figure 1). During the same period, 74% of patients with LDA ($n=678$) remained at LDA, while 44% and 25% of patients with MDA ($n=493$) or HDA ($n=146$) achieved the same target, respectively (Figure 2).

The characteristics of patients who attained LDA versus those who retained active disease are shown in Supplemental Table 3. By multivariate analysis, male sex (OR = 2.29, 95% CI: 1.62–3.23, $p<0.001$) was a positive predictor

Table 1. Patient and disease characteristics at first evaluation.

Patient characteristics	
<i>n</i>	1317
Female, <i>n</i> (%)	1012 (79%)
Age, years, mean (SD)	62.9 ± 12.6
Disease characteristics	
Disease duration, years, mean (SD)	10.3 ± 9.3
Early RA, duration <2 years	125 (10.3%)
Seropositivity, RF and/or anti-CCP, <i>n</i> (%)	696 (54%)
Erosions, <i>n</i> (%)	477 (44%)
DAS28ESR, mean (SD)	3.36 ± 1.29
HAQ, median (IQR)	0.48 (0.8)
History of arthroplasties, <i>n</i> (%)	119 (9%)
Treatment patterns	
No treatment, <i>n</i> (%)	55 (4%)
csDMARDs, <i>n</i> (%)	1112 (85%)
Monotherapy	652 (50%)
bDMARDs, <i>n</i> (%)	610 (46%)
Monotherapy	150 (11%)
Combination of cs- and bDMARDs, <i>n</i> (%)	460 (35%)
bDMARDs, <i>n</i> (%)	610 (46%)
1st agent	309 (51%)
2nd agent	158 (26%)
≥ 3 rd agent	143 (23%)
Glucocorticoids, <i>n</i> (%)	480 (36%)
Prednisolone daily dose, mg, mean (SD)	4.7 ± 3.4
Co-morbidities	
RDCI, median (IQR)	1 (2)
Current smokers	230 (18.2%)
Obesity, BMI >30 kg/m ²	283 (24.6%)
Hypertension	563 (43%)
Dyslipidemia	443 (34%)
Osteoporosis	367 (28%)
Diabetes	178 (13%)
Depression	165 (12%)
Coronary artery disease	75 (6%)
COPD	80 (6%)
Cancer, current/past	66 (5%)
Stroke	41 (3%)
anti-CCP, anti-cyclic citrullinated peptide antibodies; bDMARD, biologic DMARD; COPD, chronic obstructive pulmonary disease; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; DAS28, Disease Activity Score using 28 joints; DMARD, disease-modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; IQR, interquartile range; RA, rheumatoid arthritis; RDCI, Rheumatic Disease Comorbidity Index; RF, rheumatoid factor; SD, standard deviation.	

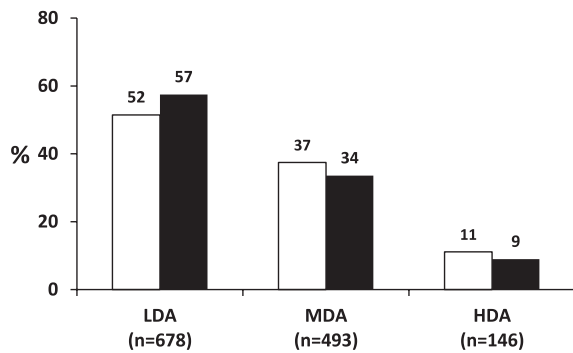


Figure 1. Disease activity at the first and second evaluation of the whole rheumatoid arthritis cohort ($n = 1317$).

The percentages (%) of patients with low (LDA; DAS28ESR < 3.2), moderate (MDA; DAS28ESR \geq 3.2 to < 5.1) and high (HDA; DAS28ESR \geq 5.1) disease activity at first evaluation (white bars) and at the end of the 1 year follow-up (dark bars) are shown.

DAS28, Disease Activity Score using 28 joints; ESR, erythrocyte sedimentation rate

of LDA while a high HAQ (OR = 0.57, 95% CI: 0.45–0.72, $p < 0.001$) and co-morbidity index (RDCI, OR = 0.86, 95% CI: 0.76–0.96, $p = 0.011$) as well as obesity (BMI > 30 kg/m², OR = 0.62, 95% CI: 0.46–0.84, $p = 0.002$) and GC use (OR = 0.75, 95% CI: 0.57–0.98, $p = 0.037$) were negative predictors (Table 2). Regarding bDMARDs, patients who had been on their \geq 2nd bDMARD were less likely to achieve LDA (OR = 0.61, 95% CI: 0.44–0.84, $p = 0.002$; Table 2). Similar results were obtained when patients with early disease were excluded (data not shown).

Clinical outcome and predictors of LDA among patients with MDA

Among patients with MDA ($n = 493$, DAS28 ESR = 3.2–5.1), 44% reached LDA (Figure 2). By multivariate analysis, male sex (OR = 2.13, 95% CI:

Table 2. Univariate and multivariate analysis of factors associated with achievement of low disease activity (DAS28ESR < 3.2) for the whole RA cohort ($n = 1317$).

Variable	Univariate analysis					Multivariate analysis			
	n	OR	95% CI		p	OR	95% CI		p
			Lower	Upper			Lower	Upper	
Sex, male	1317	2.48	1.84	3.33	<0.001	2.29	1.62	3.23	<0.001
Age	1317	0.98	0.97	0.99	<0.001	0.98	0.97	0.99	0.005
Disease duration	1219	0.98	0.97	0.99	0.035				
Seropositivity, RF/anti-CCP	1280	0.62	0.49	0.77	<0.001				
GC use	1317	0.62	0.49	0.77	<0.001	0.75	0.57	0.98	0.037
bDMARD use	1317								
1st line <i>versus</i> no bDMARD		0.92	0.7	1.2	0.53	0.84	0.62	1.16	0.3
\geq 2nd line <i>versus</i> no bDMARD		0.59	0.45	0.78	<0.001	0.61	0.44	0.84	0.002
HAQ score at first evaluation	1195	0.46	0.37	0.57	<0.001	0.57	0.45	0.72	<0.001
Co-morbidity index (RDCI)	1317	0.79	0.72	0.86	<0.001	0.86	0.76	0.96	0.011
Active smoking	1265	1.26	0.94	1.69	0.117				
Obesity, BMI > 30 kg/m²	1149	0.51	0.39	0.67	<0.001	0.62	0.46	0.84	0.002
Erosions	1317	0.66	0.51	0.84	<0.001				

Number of patients included in the final model $n = 1092$, Hosmer–Lemeshow test = 8.88 ($p = 0.35$), the model predicted correctly 67.3% of cases. Variables with statistically significant differences ($p < 0.05$) between groups by multivariate analysis are shown in bold. anti-CCP, anti-cyclic citrullinated peptide antibodies; bDMARD, biologic disease-modifying anti-rheumatic drug; BMI, body mass index; CI, confidence interval; DAS28, Disease Activity Score using 28 joints; ESR, erythrocyte sedimentation rate; GC, glucocorticoid; HAQ, Health Assessment Questionnaire; OR, odds ratio; RDCI, Rheumatic Disease Comorbidity Index; RF, rheumatoid factor.

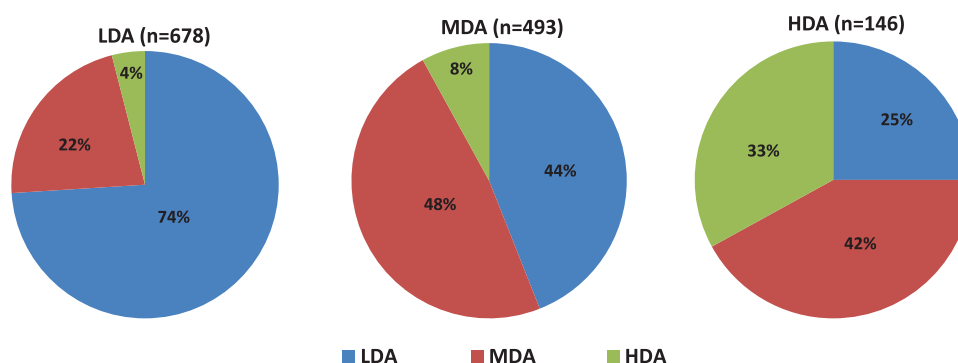


Figure 2. Disease activity outcomes according to the initial disease activity status. The percentages (%) of patients who achieved the specific outcome [low disease activity (LDA): DAS28ESR <3.2; moderate disease activity (MDA): DAS28ESR ≥3.2 to <5.1; high disease activity (HAD): DAS28ESR ≥5.1] in each patient group during the 1 year follow-up period is depicted. DAS28, Disease Activity Score using 28 joints; ESR, erythrocyte sedimentation rate

Table 3. Univariate and multivariate analysis of factors associated with achievement of low disease activity (DAS28ESR <3.2) among patients with moderate disease activity (n=493).

Variable	Univariate analysis					Multivariate analysis			
	n	OR	95% CI		p	OR	95% CI		p
			Lower	Upper			Lower	Upper	
Sex, male	493	2.15	1.32	3.51	0.002	2.13	1.30	3.99	0.004
Age	493	0.99	0.98	1.01	0.98	1.002	0.98	1.02	0.81
Working status, <67years	444	1.59	1.02	2.48	0.041				
bDMARD use									
1st line versus no bDMARD	493	0.86	0.55	1.34	0.50				
≥2nd line versus no bDMARD		0.60	0.38	0.93	0.22				
HAQ score at first evaluation	433	0.7	0.49	1.001	0.051				
Co-morbidity index, RDCI	493	0.87	0.75	1.009	0.065	0.81	0.68	0.97	0.024
History of serious infection	493	0.49	0.27	0.89	0.018				
“Lower” versus “Higher” MDA status	493	2.03	1.40	2.95	<0.001	1.93	1.27	2.94	0.002

Number of patients included in the final model=407. Variables with statistically significant differences ($p < 0.05$) between groups by multivariate analysis are shown in bold. “Higher” moderate disease activity (MDA) status=DAS28ESR, 4.2–5.1; “Lower” MDA status=DAS28ESR: 3.2–4.1. bDMARD, biologic disease-modifying anti-rheumatic drug; CI, confidence interval; DAS28, Disease Activity Score using 28 joints; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; OR, odds ratio; RDCI, Rheumatic Disease Comorbidity Index.

1.3–3.99, $p=0.004$) and a lower co-morbidity index (RDCI, OR=0.81, 95% CI: 0.68–0.97, $p=0.024$) were independently associated with LDA, as was the case for the entire RA cohort (Table 3). Additionally, for this subgroup of patients, a “lower” (DAS28ESR: 3.2–4.1) MDA status (OR=1.93, 95% CI: 1.27–2.94, $p=0.002$)

at first evaluation was a positive predictor of LDA (Table 3). Similar results were obtained when patients with early disease were excluded (data not shown).

Overall, “lower” MDA patients had a higher chance of achieving LDA (51%) compared with

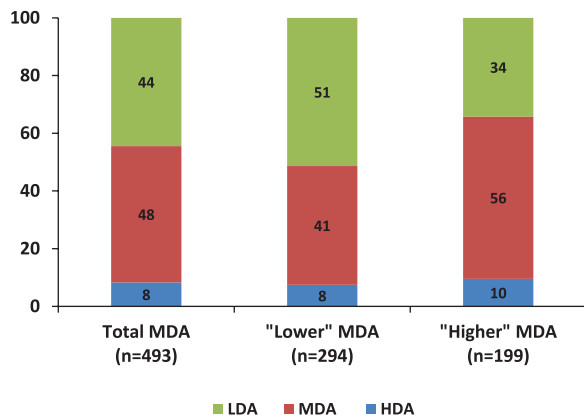


Figure 3. Outcomes among patients with moderate disease activity (MDA; $n=493$). The clinical outcomes of patients with MDA (DAS28ESR: ≥ 3.2 to <5.1) as a total group ($n=493$) and those with "lower" (DAS28ESR: $3.2-4.1$, $n=294$) or "higher" (DAS28ESR: $4.2-5.1$, $n=199$) MDA status during the 1 year follow-up are shown. DAS28, Disease Activity Score using 28 joints; ESR, erythrocyte sedimentation rate

the "higher" MDA ones (34%, $p=0.0002$; Figure 3) while the rates of worsening to HDA were similar between the two groups (8% and 10%, respectively, $p=0.51$).

bdMARD pattern use

Current treatment Guidelines and Recommendations support bdMARD initiation (among csDMARD users) or switching (in bdMARD users) in RA patients who do not achieve their treatment targets.^{3,8,9} Overall, the rate of bdMARD initiation or switching among csDMARD and bdMARD users was 14% (91/652) and 16% (98/610), respectively (Figure 4). More specifically among patients with active disease (DAS28ESR >3.2), the respective rates were 21% (62/292) and 22% (68/315). These rates were higher among HDA patients compared with those with MDA (bdMARD initiation: 39% versus 17%, $p=0.0005$, bdMARD switching: 36% versus 17%, $p=0.0008$).

We finally studied the bdMARD pattern use according to disease duration. Among patients who were on csDMARDs at first evaluation, we did not notice any difference in the rates of bdMARD initiation between those with and those without early disease (defined as ≤ 2 years), neither in the total cohort of csDMARD users (12.5% versus 12.4%, $p=0.98$) nor in those csDMARD users not in remission (11.1% versus 9.6%, $p=0.3$). In general, those with active

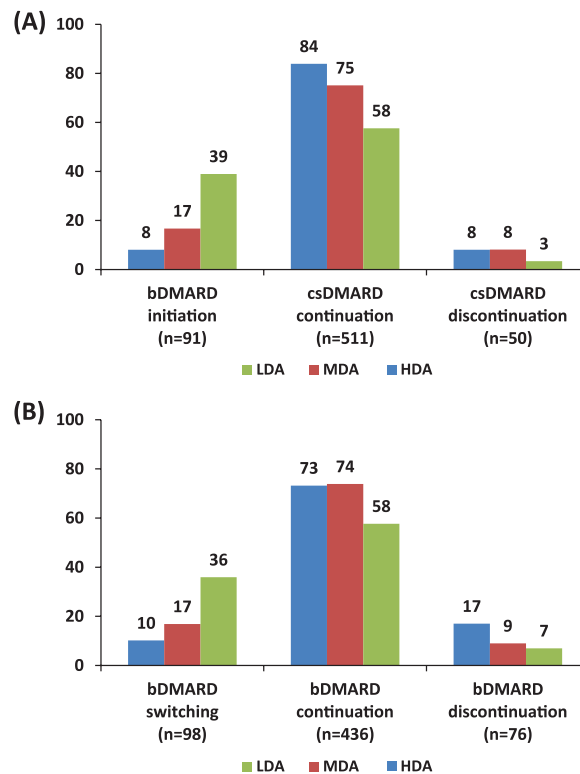


Figure 4. (A) Changes in DMARD use among csDMARD ($n=652$) or (B) bdMARD users ($n=610$). LDA, low disease activity: DAS28ESR <3.2 ; MDA, moderate disease activity: DAS28ESR ≥ 3.2 to <5.1 ; HDA, high disease activity: DAS28ESR ≥ 5.1 .

disease who started bdMARDs were younger compared with those who did not (61.7 ± 10.7 versus 64.9 ± 12 years, $p=0.055$).

When we performed the same analysis in bdMARD users, a statistically significant difference in the respective rates of bdMARD switching was found both in the total bdMARD cohort (34.8% versus 17.4%, $p=0.03$) and those not in remission (43.8% versus 23.4%, $p=0.049$).

Discussion

The primary goals of our prospective RA cohort study were two-fold: first to assess the rate of achievement of current treatment targets (LDA or remission) and second to track changes in treatment patterns (mainly initiation or switching of a bdMARD) in real-life settings. In contrast to previous inception or early RA cohorts, most of our patients had long standing (mean duration: ~ 10 years) disease with frequent presence of co-morbidities, treated both with csDMARDs and bdMARDs (46%). This context is

important, since older studies have described not only gene expression differences in peripheral blood mononuclear cells and synovial tissue between early and longstanding RA,^{16,17} but also attenuated responses to anti-rheumatic therapies.¹⁸

Regarding our first goal, at our initial cross-sectional evaluation more than half of our patients (52%) had already achieved the treatment targets of LDA/remission. Although this is an important achievement, it should be noted that in a large cohort of real-life RA patients (mainly from referral centers) where bDMARDs were used in 46% of cases, the rate of residual active disease (48%) remains high. This rate is somewhat lower from what has been recently reported from other RA registries worldwide (range: 58–76%).¹⁹ For example, in the US CORRONA registry among 24,176 RA patients (with 38% bDMARD use), 58% of patients had still active disease (DAS28ESR \geq 3.2).²⁰

One year later, a small but statistically significant increase in the proportion of patients who achieved LDA was noted (57%; +5%). During this period, the overall rate of bDMARD initiation (among csDMARD users) or switching (among bDMARD users) was rather low at 14% and 16%, respectively. However, these low annual rates of bDMARD initiation or switching in real life prevalent RA cohorts are close to the ones reported recently from US insurance databases (11% and 17%, respectively).²¹ Even among patients with active disease (DAS28ESR \geq 3.2), only one out of five RA patients started or switched their bDMARD. Although it is expected that in prevalent patients with long-standing RA, such therapy changes may be less frequent than in newly diagnosed incident cases, nevertheless our findings emphasize that a significant proportion of RA patients (~43%) in real life fail to achieve the recommended treatment target and thus a more aggressive treatment approach is needed.

A number of reasons for not complying with T2T strategies have been proposed. For example, rheumatologists in the CORRONA registry were more reluctant to initiate bDMARDs in older patients²² as was the case in our study. Other factors, such as patients' preferences, concerns for potential treatment-related complications or patient–physician discordances in disease activity assessment²³ could also play a role.

In the entire RA cohort, we identified, by multivariate analysis, male sex as a positive and older age, obesity (BMI > 30 kg/m²), high HAQ and comorbidity burden as well as use of GCs or \geq 2 bDMARDs as negative predictors of low DAS28 1 year later.

Whether or not gender is an important factor in determining treatment responses in RA is currently unclear.^{24–26} Recently, data from the British Society for Rheumatology Biologics Register–RA, have shown that female gender was a negative predictor of sustained remission and LDA in anti-tumor necrosis factor (TNF) treated RA patients.²⁷ Couderc *et al.* showed higher rates of remission after rituximab therapy in men but only in the setting of previous anti-TNF failure,²⁴ whereas in the Oencia and Rheumatoid Arthritis registry, there was no difference in response to abatacept between men and women.²⁵ However, DAS28, tender joint count and patient global assessment were consistently lower in men during follow-up.²⁵ In a study from Italy that included RA patients treated with 1st line anti-TNFs, male gender was associated with higher odds of remission/LDA after 2 years,²⁸ while similar findings were reported in a recent meta-analysis.²⁹ Although previous studies had attributed these discrepancies to subjective rather than objective components of disease activity metrology and not to RA itself,²⁶ our data suggest that gender may have an impact in treatment responses in RA patients.

In our RA cohort, we found also that obesity, which was a common co-morbidity (24.6%), represented a negative predictor of LDA at 1 year of follow-up (OR = 0.6). These findings are in accordance with two previous meta-analyses^{30,31} and recent UK studies,^{27,32} showing that obese RA patients are less likely to achieve remission compared with non-obese or normal weight patients. It remains though unclear at the moment whether there is true association between obesity and inadequate treatment responses or whether obesity could bias disease activity measurements such as DAS28.³³ In a recent post-hoc analysis of two randomized controlled trials (RCTs) of RA patients treated with golimumab, George *et al.* showed that although obese RA patients had a lower chance of achieving DAS28 remission compared with non-obese, their likelihood to reach low synovitis and inflammation scores, as measured subjectively by MRI, was similar between the two groups.³⁴ Certainly more prospective

long-term data with objective and subjective measurements of disease activity are needed before a final conclusion can be made.

Co-morbidities are common in RA patients worldwide^{15,35–37} and impact significantly upon treatment decisions and disease outcomes in real-life settings,^{28,38–41} since in RCTs such patients are usually excluded. In our RA cohort, co-morbidities were also very common (63%) and their presence decreased the chance of reaching LDA. This finding emphasizes the difficulties that physicians are facing in making treatment decisions and achieving treatment targets in daily clinical practice.

As for the role of treatment on disease activity control, we found that GC users were less likely to achieve LDA. Indeed, several studies have shown that although GCs may contribute to more rapid disease control at therapy initiation,⁴² their efficacy in maintaining remission is questionable.⁴³ We also showed that patients being treated with second or higher line of biologics were also less likely to achieve LDA. This could be due to either physicians' reluctance to switch bDMARDs in patients that have already failed at least one bDMARD or the presence of resistant, long-standing disease.

A novel finding of our study has to do with the analysis of predictors of response in patients with MDA (DAS28ESR = 3.2–5.1). This patient subgroup represents probably the most common RA subgroup in real-life settings with a recent review of five RA registries worldwide estimating its frequency at ~40% (range: 25–53%).¹⁹ Previous studies in patients with early RA have shown that persistent MDA is associated with worse clinical, functional and radiological outcomes compared to patients with LDA,^{10–12} while a recent RCT of MDA patients who had not responded to methotrexate showed that combination therapy of a csDMARD (methotrexate) with a bDMARD (etanercept) was more efficacious in inducing and maintaining LDA compared with csDMARD (methotrexate) monotherapy.⁴⁴ These data indicate that aggressive therapy is efficacious for this group of patients.

Nevertheless, real-life, longitudinal data for MDA patients with established RA are limited. In our cohort, 37% of patients had MDA and 1 year later, 44% of them had achieved LDA/remission. By multivariate analysis, as for the whole RA cohort, male sex and a lower co-morbidity

burden were independently associated with a good clinical outcome at 1 year.

In addition, for this group of patients a “lower” MDA status (DAS28ESR = 3.2–4.1) at first evaluation was another independent factor associated with transition to LDA. A recent analysis of 1274 csDMARD-treated RA patients with MDA from the British Registry, showed that seven different trajectory groups according to disability score (HAQ) could be distinguished which, during a 3 year follow-up period, remained rather stable.⁴⁵ Our data, in accordance to these findings, may indicate the existence of distinct patient subgroups with a different clinical outcome within the MDA group. Whether or not this “lower” disease activity subgroup has a more benign course, responding better to DMARDs, is currently uncertain.

On the other hand, it should be mentioned that half of patients with “lower” MDA status do not achieve LDA after 1 year of follow-up. This could be due to the fact that physicians choose a more conservative approach and are reluctant to intensify therapy by initiating or switching bDMARDs (17% overall rate) in these patients. Well-designed prospective studies are needed in order to define the natural course and response to therapy of these MDA subgroups, before any change in existing treatment recommendations is made.

Our study has certain strengths and limitations. Its strengths include the high number of included patients, its prospective and multicenter nature, the inclusion of patients with established disease who were being treated with cs- and/or bDMARDs in a real-life setting and the specific focus on the MDA patient subgroup.

Regarding its limitations, loss to follow-up and missing data are inarguable concerns in real-life prospective patient cohorts. In our case, follow-up evaluation was not available in 38% of patients. Although undesirable, these loss to follow-up rates are not infrequent in real-life observational studies of patients not only with rheumatic diseases (24–35%),⁴⁶ but also in other settings, such as post-operatively after spine surgery (59%).⁴⁷ Moreover, 15% of patients were excluded from final analysis due to missing disease activity data, a percentage similar to or even lower from other RA registries.^{36,48} Their characteristics, though, did not differ significantly from those who were analyzed. Another issue was the absence of a specific therapeutic protocol followed by all centers

with the potential of heterogeneity in treatment decisions. This is the issue, though, in most RA registries worldwide, while it should be noted that since 2009 the Greek Rheumatology Society has been regularly issuing updated recommendations for RA management and its therapeutic algorithm has been implemented in the obligatory electronic prescription of anti-rheumatic therapies over the last 6 years. Last, since most of our patients had been recruited from hospital referral centers, this could have created a “referral bias” with inclusion of the most severe, difficult to treat cases with more frequent use of bDMARDs compared with the general RA patient population.

In conclusion, our prospective, real-life RA study clearly shows that 20 years after the introduction and widespread implementation of biologics in clinical practice, a significant proportion of RA patients with established disease (~40%) do not achieve the predefined treatment targets of LDA or remission. In contrast to early, incident RA cohorts, the annual rates of bDMARD initiation or switching among RA patients with active disease were rather low (~20%), emphasizing the need for better compliance with existing treatment Recommendations and Guidelines. Furthermore, we observed that approximately one-third of patients remain in moderately active disease despite therapy with cs- and/or bDMARDs, while within this group, a subgroup of patients at the lower end of disease activity (DAS28ESR = 3.2–4.1) had a higher likelihood of reaching low DAS28.

Overall, our findings demonstrate that there are still a number of unmet therapeutic needs in real-life settings while at the same time they indicate that MDA subgroups according to their disease activity level deserve to be studied further.

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The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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