Rheumatology International (2021) 41:1915–1924
https://doi.org/10.1007/s00296-021-04939-8

Rheumatology
INTERNATIONAL

COHORT STUDIES

In the era of disease-modifying antirheumatic drugs, how close are we to treating rheumatoid arthritis without the use of glucocorticoids?

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Received: 3 May 2021 / Accepted: 28 June 2021 / Published online: 5 July 2021

Abstract

We wanted to see how close we could get to our goal of treating rheumatoid arthritis (RA) without the use of glucocorticoids (GCs) in the disease-modifying antirheumatic drugs (DMARDs) era using real-life data. Established in 2017, the TReasure database is a web-based, prospective, observational cohort for Turkey. As of May 2019, there were 2,690 RA patients recorded as receiving biologic and targeted synthetic DMARDs (bDMARDs and tsDMARDs) therapy. At the start of the bDMARDs or tsDMARDs, patients with follow-up visits of at least 3 months were registered. At the time of registration and the last visit, doses of GCs were recorded and it was determined if the target dose of ≤ 7.5 mg was achieved. During registration and follow-up, 23.4% of the patients did not receive GCs and 76.5% of the patients received GCs at any time. GCs could be stopped after 59 (25–116) months in 28.4% of these patients, but 71.6% of patients were still using GC. The target GC dose could not be achieved in 18.2% of these patients ($n = 352$). The rate of continuing to use GC was significantly higher in women, in the elderly, those with rheumatoid factor (RF) positive, with higher Visual Analog Scale (VAS) pain and Disease Activity Score (DAS)-28. The initial GC dose of ≥ 7.5 mg/day was found to be crucial in not reaching the GC target dose ($p < 0.001$, OR 39.0 (24.1–63.2)). The initial GC dose of ≥ 7.5 mg/day, female gender, age, RF positivity, high DAS28, and VAS pain level were all highly related for GC continuation. Despite the use of DMARDs, our data revealed that we are still far from achieving our goal of treating RA without using steroids.

Keywords DMARDs · Glucocorticoids · Rheumatoid arthritis · Target dose · TReasure

Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory and systemic autoimmune disease [1, 2]. Current treatment of RA includes synthetic disease-modifying antirheumatic drugs (DMARDs) particularly the use of methotrexate, leflunomide, and sulfasalazine alone or in combination. In case of unresponsiveness to these therapies, biological DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) are used [1, 3, 4]. At the onset of RA, glucocorticoids (GCs) can be used as a bridge therapy to control joint-related complaints [1, 2, 5–7]. There are also studies revealing that in addition to controlling disease activity, GCs reduce radiological progression [8, 9]. In RA, the rate of GC use as the initial therapy ranges from 48 to 77% [10]. As was stated by Hardy et al. in 2018, although GCs, a class of drugs that are crucial in RA treatment, is known for almost 70 years, their mechanism of action has only been initiated to be recognized recently [11].

Recommendations for the treatment of RA, which was published in 2013 by European League against Rheumatism (EULAR), were updated in 2019 [12]. These updated recommendations comprise critical regulations on the use of GCs when compared to 2013 suggestions, however, the recommendation on GCs has not changed since 2016. While GCs were recommended to be used at the "smallest dose possible" in 2013, they were recommended to be discontinued "in the shortest time" possible in 2019 [2, 12, 13].

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Although the EULAR recommended that GCs should be used at the smallest dose for the shortest time possible, data on the use of GCs in daily practice are limited. The TReasure database is a web-based database established in 2017 with the participation of 17 centers from different regions of Turkey. The TReasure registry includes the data of RA patients receiving tsDMARDs or bDMARDs. The present study aimed to investigate the use of GCs in RA patients at initial diagnosis, characteristics of the patients who were discontinued from GCs during the follow-up, and the use of GCs in the last visits of the patients and the related factors.

Methods

TReasure database and patients

The TReasure database, which was established in 2017, is a web-based, prospective, observational cohort including RA and spondyloarthritis (SpA) patients from 17 centers in different regions of Turkey (13). Patient data entry in the centers was started in December 2017 and as of May 2019, data of 7,332 patients receiving tsDMARDs or bDMARDs were recorded in the database. Of these patients, 2,690 had RA, 4,264 had SpA, and 378 had psoriatic arthritis. Patients with at least 3-month follow-up visits were included. Data on the use of GCs were not available in 162 of 2,690 RA patients recorded in the TReasure database. For this reason, analyses were performed using the data of 2,528 RA patients. To perform the present research, the approval for the TReasure database was obtained from the Ethics Committee of Hacettepe University in May 2017 (KA17/058) and from the Republic of Turkey Ministry of Health in October 2017 (93189304–14.03.01). Written informed consent of all patients was obtained.

Data of RA patients

Each patient was diagnosed with RA by his/her responsible clinician. The following patients' data were recorded: age, gender, disease duration, and the positivity for rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibodies, smoking status, body mass index, and comorbid conditions. Disease activity parameters at the time of initiation to the first tsDMARD or bDMARD were recorded. These parameters included erythrocyte sedimentation rate (ESR) (mm/h), C-reactive protein (CRP; mg/L), number of swollen joints (66 joints), number of tender joints (68 joints), the Health Assessment Questionnaire–Disability Index (HAQ-DI) scores, pain-Visual Analog Scale (VAS, 0–100 mm) score, fatigue-VAS score (0–100 mm), and the patient global activity assessment (PtGA)-VAS score (0–100 mm). As the composite indices, the Disease Activity Score (DAS)-28, the Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI) were used. The biological DMARDs included in the TReasure database were anti-tumor necrosis factor (TNF) drugs (adalimumab, infliximab, golimumab, certolizumab, or etanercept), abatacept, rituximab, tocilizumab, and/or targeted synthetic DMARD included in the TReasure database was tofacitinib.

Classification of GCs and target GC dose

The doses of GCs were recorded at the time of registration and in the last visit after a mean 59 (25–116) months' follow-up. Time of registration was always defined at the start of the first bDMARD or tsDMARD and at that time the dose of GCs used was recorded. At the same time, when and at what doses these GCs were started was questioned. Although the doses of the GCs were increased or decreased based on the clinical activity of the RA patients during the follow-up, it is hardly possible to record these dose titrations retrospectively. In the last visit of the patients, it was also recorded whether the patients achieved the target GC dose or not. The doses of GCs were recorded as the prednisone equivalent dose as follows: ≤ 2.5 mg, > 2.5 mg $- < 7.5$ mg, 7.5–15 mg, and > 15 mg. The target dose for GCs recommended by the EULAR is ≤ 7.5 mg prednisone (2, 13, 15). In the present study, the RA patients were divided into 4 groups according to their GCs use as follows: (1) those who did not receive GCs during registration and follow-up ($n = 592$), (2) those received GCs at any time ($n = 1{,}936$), (3) those who were currently receiving GCs ($n = 1{,}386$), and (4) those who discontinued GCs (n = 550).

Statistical analysis

Statistical analyses were performed using the Predictive Analytics Software (PASW) 18.0 (SPSS Inc., Chicago, IL, USA) for Windows. Normality of data was tested using the visual (histogram and probability plots) and analytical (Kolmogorov–Smirnov/Shapiro–Wilk tests) methods. Descriptive statistics (i.e., mean, standard deviation) and frequency distributions were used to report the characteristics of the patients. Categorical variables were expressed as numbers and percentages and numerical variables were expressed as median, 25th, and 75th percentiles (Q1 and Q3). The Chi-square test was used for two-group comparisons and multiple comparisons, where appropriate. However, when the Chi-square condition was not met, Fisher's exact test was used for two-group comparisons. The Mann–Whitney *U* test was used to compare non-normally distributed variables between two independent groups. Fort the multivariate analysis, the possible factors identified with univariate analyses were further entered into the logistic regression

analysis to determine independent predictors for not achieving the GC target dose. A p value of < 0.05 was considered statistically significant.

Results

Comparison of the RA patients those who did not receive GCs during registration and follow-up with those who received GCs at any time

Data of 2,528 patients with available information on GC use in the TReasure database were analyzed. 23.4% of these patients did not receive GCs during registration and follow-up. The status of RA patients according to their GC use at the time of registration and in the last visit is demonstrated in Fig. 1.

The differences between the patients who received GCs at any time and those who did not receive GCs during registration and follow-up in terms of demographic characteristics and comorbidities are demonstrated in Table 1. The number of seronegative patients was higher in the group those who did not receive GCs during registration and follow-up. Evaluation of the disease activity of the patients at the time of initiation to the first bDMARD or tsDMARD revealed that the ESR and CRP values and the HAQ-DI scores were similar in the two groups; however, the scores of the composite disease indices (the CDAI, SDAI, and DAS-28) were higher in the group that received GCs. The anti-TNF therapies were mostly preferred as biological DMARDs in the patients who did not receive GCs during registration and follow-up; on the other hand, regarding the non-TNF biological DMARD use in this group, the use of abatacept was lower and the use of tocilizumab was higher. Besides, it was observed that synthetic DMARDs were used less commonly in this group. Among comorbidities, Sjögren's syndrome was more frequent in the patients who received GCs at any time. Similarly, the rates of hypertension, hyperlipidemia, and asthma were also higher in the patients who received GCs at any time; on the other hand, the groups did not differ in terms of the presence of diabetes mellitus.

Initial and final doses of GCs in the RA patients

The percentages of RA patients who received an initial GC dose of 0 mg, ≤ 2.5 mg, 2.5–7.49 mg, 7.5–15 mg, and > 15 mg were 23.4%, 4.0%, 46.3%, 19.8%, and 6.4%, respectively. The patients who received an initial GC dose

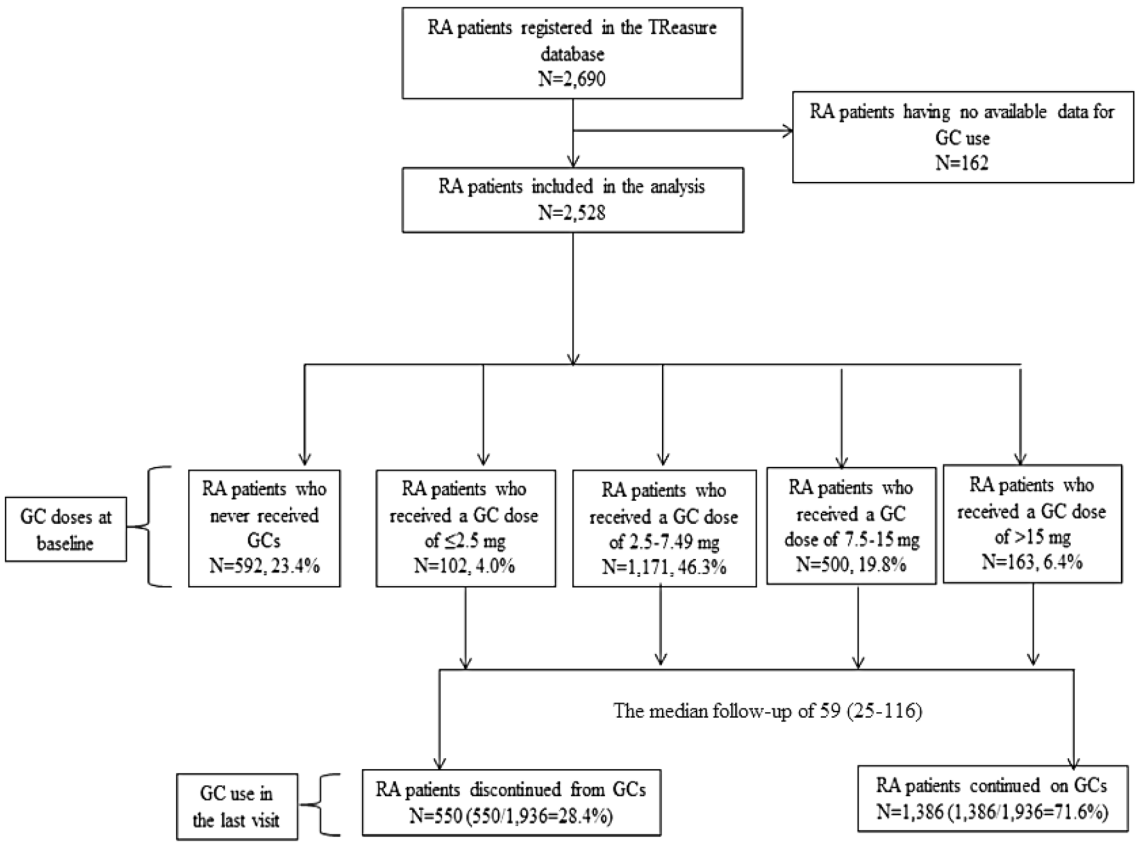

Fig. 1 The status of rheumatoid arthritis (RA) patients according to their glucocorticoid (GC) use at the time of registration and in the last visit

Table 1 Baseline characteristics of the rheumatoid arthritis (RA) patients who did not receive GC during registration and follow-up and who received GCs

Characteristics	RA patients who did not receive GCs during registration and follow-up ($n=592$)	RA patients who received GCs at any time ($n=1936$)	p
Female sex, %	76.5	79.7	0.097**
Age, median (Q1-Q3)	55 (45–63)	55 (43–63)	0.520*
BMI, kg/m^2, median (Q1–Q3)	27.0 (23.9–31.2)	27.9 (24.3–32.5)	**0.004***
Disease duration, year, median (Q1–Q3)	13 (7–22)	10 (6–16)	**< 0.001***
RF, *n*/*N* (%)	246/425 (57.9)	1,228/1,808 (67.9)	**< 0.001****
Anti-CCP, *n*/*N* (%)	177/342 (51.8)	846/1,376 (61.5)	**< 0.001****
RF or anti-CCP, *n*/*N* (%)	281/426 (66.0)	1,364/1,852 (73.7)	**0.001****
ESR mm/h, median (Q1–Q3)	35 (17–54)	32 (17–52)	0.352*
CRP mg/l, median (Q1–Q3)	13.7 (5–33.5)	14.8 (6.07–36)	0.099*
HAQ-DI, median (Q1–Q3)	0.8 (0.6–1.1)	0.9 (0.5–1.4)	0.161*
CDAI, median (Q1–Q3)	15 (12–18)	19 (12–31)	**0.001***
SDAI, median (Q1–Q3)	29 (19–52)	38 (23–61)	**0.008***
DAS-28 (CRP), median (Q1–Q3)	3.04 (1.82–4.13)	3.77 (2.72–4.98)	**< 0.001***
VAS Pain, median (Q1–Q3)	70 (50–75)	70 (50–80)	**0,001***
VAS Fatigue, median(Q1–Q3)	60 (40–70)	70 (50–80)	**< 0,001***
Secondary Sjögren's syndrome, *n*/*N* (%)	6/252 (2.4)	78/1,107 (7.0)	**0.006****
Interstitial lung disease, *n*/*N* (%)	9/146 (6.2)	42/574 (7.3)	0.628**
Hypertension, *n*/*N* (%)	107/428 (25.0)	589/1,921 (30.7)	**0.020****
Diabetes mellitus, *n*/*N* (%)	48/426 (11.3)	217/1,925 (11.3)	0.998**
Hyperlipidaemia, *n*/*N* (%)	38/420 (9.0)	308/1,837 (16.8)	**< 0.001****
Asthma, *n*/*N* (%)	13/418 (3.1)	124/1,860 (6.7)	**0.006****
Thyroid diseases, *n*/*N* (%)	29/424 (6.8)	228/1,895 (12.0)	**0.002****
Osteoporosis, *n*/*N* (%)	15/39 (38.5)	105/254 (41.3)	0.734**
Anaemia, *n*/*N* (%)	89/224 (39.7)	585/1,134 (51.6)	**0.001****
Coronary artery diseases, *n*/*N* (%)	19/469 (4.1)	100/1,859 (5.4)	0.243**
Thromboembolic events, *n*/*N* (%)	0/289 (0)	13/989 (1.3)	0.050**
GIS bleeding, *n*/*N* (%)	7/472 (1.5)	15/1,875 (0.8)	0.169**
Cancer, *n*/*N* (%)	7/484 (1.4)	36/1,902 (1.9)	0.510**
Anti-TNF, *n* (%)	385 (65.0)	1,019 (52.6)	**< 0.001****
Abatacept, *n* (%)	76 (12.8)	374 (19.3)	**< 0.001****
Rituximab, *n* (%)	109 (18.4)	328 (16.9)	0.408**
Tocilizumab, *n* (%)	114 (19.3)	238 (12.3)	**< 0.001****
Tofacitinib, *n* (%)	71 (12.0)	266 (13.7)	0.274**
Methotrexate, *n* (%)	261 (44.1)	1,764 (91.1)	**< 0.001****
Hydroxychloroquine, *n* (%)	199 (33.6)	1,517 (78.4)	**< 0.001****
Leflunomide, *n* (%)	190 (32.1)	1,186 (61.3)	**< 0.001****
Sulfasalazine, *n* (%)	184 (31.1)	1,107 (57.2)	**< 0.001****

RA, rheumatoid arthritis; *GCs*, glucocorticoids; *BMI*, body mass index; *Q1–Q3,* 25th percentile–75th percentile; *RF*, rheumatoid factor; *CCP*, cyclic citrullinated peptide; *ESR*, erythrocyte sedimentation rate; *CRP*, C-reactive protein; *HAQ–DI*, Health Assessment Questionnaire–Disability Index; *CDAI*, Clinical Disease Activity Index; *SDAI*, Simplified Disease Activity Index; *DAS-28*, Disease Activity Score-28; *GIS*, gastrointestinal; *TNF*, tumor necrosis factor; *VAS*, Visual Analogue Scale

*Mann–Whitney *U* test

**Chi-square test

***Fisher's test

Values with $p < 0.05$ were highlighted in bold

of > 15 mg were compared with those who received an initial GC dose of < 15 mg. The median disease duration was shorter (9 years [Q1-Q3, 4–15 years] vs. 10 years [Q1-Q3, 6–17 years], $p = 0.005$), comorbid interstitial lung disease was more common (20.4% vs. 6.1%, $p < 0.001$), the median ESR (40 [Q1–Q3, 21–62] vs. 32 [Q1–Q3, 17–51], $p = 0.001$) and the median CRP value (21.5 [Q1–Q3, 8–63.1] vs. 14.2 [Q1-Q3, 5.84–34.1], p = 0.001) at the time of initiation to bDMARDs or tsDMARD were higher, and the median DAS-28-ESR was higher (4.4 [Q1–Q3, 3.35–5.97] vs. 3.95 [Q1–Q3, 3.14–5.27), $p = 0.015$) in the patients who received an initial GC dose of > 15 mg.

The median follow-up duration of the patients was 59 (25–116) months. The initial and final GC doses of the patients who received GCs at any time are demonstrated in Table 2. 352 patients received a final GC dose of ≥ 7.5 mg/day. The target GC dose could not be achieved in 18.1% of the patients who received GC at any time ($n = 1,936$) and in 13.9% of the overall patient group (n = 2,528). The final GC dose was ≥ 7.5 mg in 48.2% ($n = 320$) of the patients who received an initial GC dose of ≥ 7.5 mg ($n = 663$) and in 2.5% ($n = 32$) of the patients who received an initial GC dose of ≤ 7.5 mg ($n = 1,273$) ($p < 0.0001$). Moreover, the mean duration of disease was shorter (8 years [Q1–Q3, 4–14 years] vs. 10 years [Q1–Q3, 6–16 years], $p < 0.001$) and the median HAQ-DI score was higher (1 [Q1–Q3, 0.6–1.45] vs. 0.9 [Q1–Q3, 0.5–1.4], $p = 0.042$) in the patients who received an initial GC dose of ≥ 7.5 mg (Table 3). To assess the factors that might predict achieving the target dose, a regression analysis was performed including the following variables: gender, presence of smoking, initial GC dose being ≥ 7.5 mg, disease duration, the HAQ-DI score, and ESR before using

Table 2 Distribution of the patients who received GCs at any time ($N = 1,936$) according to their initial and final GC doses

	Initial dose (mg)				*n* (%)
	≤ 2.5	> 2.5 to < 7.5	7.5–15	> 15	
Final dose (mg)					
0	31	383	103	33	550 (28.4)
≤ 2.5	48	67	20	2	137 (7.1)
2.5–7.49	19	693	149	36	897 (46.3)
7.5–15	4	24	224	44	296 (15.3)
> 15	0	4	4	48	56 (2.8)
Total, *n* (%)	102 (5.3)	1171 (60.4)	500 (25.8)	163 (8.4)	

Table 3 Comparison of patients in terms of final GC dose (< 7.5 mg OR ≥ 7.5 mg)

	The final GC dose was < 7.5 mg	The final GC dose was ≥ 7.5 mg	*p*
Female sex, %	1273/1584 (80.4)	270/352 (76.7)	0.122
Male sex, %	311/1584 (19.6)	82/352 (23.3)	
Age, median (Q1–Q3)	55 (43–63)	54 (43–62)	0.433
BMI, kg/m2, median (Q1–Q3)	27.97 (24.245–32.44)	28.265 (24.34–33.37)	0.380
Presence of smoking, %	333/1557 (21.4)	88/349 (25.2)	0.119
Disease duration, year, median (Q1–Q3)	10 (6–16)	8 (4–14)	**< 0.001**
Initial GC dose being ≥ 7.5 mg	343/1584 (21.7)	320/352 (90.9)	**< 0.001**
RF, *n* (%)	472/1478 (31.9)	108/330 (32.7)	0.780
Anti-CCP, *n* (%)	424/1114 (38.1)	106/262 (40.5)	0.473
ESR mm/h, median (Q1–Q3)	31 (16–51)	35.5 (20–53)	0.065
CRP mg/l, median (Q1–Q3)	14.5 (5.94–35.3)	15.8 (7–42)	0.170
HAQ-DI, median (Q1–Q3)	0.9 (0.5–1,4)	1 (0.6–1.45)	**0.042**
CDAI, median (Q1–Q3)	19 (12.5–31)	15,75 (11–30.25)	0.526
SDAI, median (Q1–Q3)	38.5 (23.9–61)	35 (19.5–64)	0.537
PtGA-VAS, median (Q1–Q3)	70 (50–80)	70 (50–80)	**0.017**
Pain-VAS, median (Q1–Q3)	70 (50–80)	70 (50–80)	0.191
DAS-28 (ESR), median	4.035 (3.165–5.32)	4.335 (3.39–5.54)	**0.034**
DAS-28 (CRP), median	3.72 (2.68–4.94)	3,895 (2.845–5.07)	0.070

GCs, glucocorticoids; *BMI*, body mass index; *Q1–Q3*, 25th percentile–75th percentile; *RF*, rheumatoid factor; *CCP*, cyclic citrullinated peptide; *ESR*, erythrocyte sedimentation rate; *CRP*, C-reactive protein; *HAQ–DI*, Health Assessment Questionnaire–Disability Index; *CDAI*, Clinical Disease Activity Index; *SDAI*, Simplified Disease Activity Index; *DAS-28*, Disease Activity Score-28; *PtGA*, patient global activity assessment; *VAS*, Visual Analogue Scale

Values with $p < 0.05$ were highlighted in bold

bDMARDs or tsDMARD. Accordingly, only the initial GC dose of ≥ 7.5 mg/day (odds ratio [OR], 39.0 [24.1–63.2]) was determined as a risk factor for not achieving the GC target dose recommended by the EULAR.

Characteristics of the RA patients who discontinued and continued GCs during the follow-up

At the end of the follow-up period of 59 (25–116) months of 1936 patients who received GCs, GCs were

Table 4 Characteristics of the patients who discontinued and continued GC therapy during the follow-up period

	RA patients who continued GCs ($n=1386$)	RA patients who discontinued GCs ($n=550$)	p
Female sex, %	1,123 (81)	420 (76.4)	**0.021****
Age, median (Q1–Q3)	55.5 (44–63)	52 (40–63)	**< 0.001***
BMI, kg/m^2, median (Q1–Q3)	28.23 (24.39–32.87)	27.61 (24.09–32.1)	0.102*
Disease duration, year, median (Q1–Q3)	10 (5–16)	9 (6–15)	0.743*
RF, *n* (%)	908 (70)	320 (62.6)	**0.002****
Anti-CCP, *n* (%)	618 (61.6)	228 (61.3)	0.929**
ESR mm/h, median (Q1–Q3) (Initial visit)	33 (17–51)	30 (17–54)	1.000*
CRP mg/l, median (Q1–Q3) (Initial visit)	14.9 (6–38)	14.55 (6.4–30.1)	0.762*
HAQ-DI, median (Q1-Q3) (Initial visit)	0.9 (0.55–1.4)	0.85 (0.45–1.35)	0.129*
CDAI, median (Q1–Q3) (Initial visit)	19 (13–31)	15 (11–29)	0.096*
SDAI, median (Q1–Q3) (Initial visit)	40 (24–65)	36 (21–55)	0.222*
PtGA-VAS, median (Q1- Q3) (Initial visit)	70 (50–80)	60 (50–80)	**0.002***
Pain-VAS, median (Q1–Q3) (Initial visit)	70 (50–80)	60 (50–80)	**0.001***
DAS-28 (ESR) (initial visit), median (Q1–Q3)	4.15 (3.25–5.47)	3.90 (3.08–5.15)	**0.021***
DAS-28 (ESR) (last visit), median (Q1-Q3)	2.98 (2.24–3.89)	2.64 (2.02–3.41)	**< 0.001***
DAS-28 (CRP) (initial visit), median (Q1–Q3)	3.84 (2.77–5.08)	3.51 (2.66–4.61)	**0.026***
DAS-28 (CRP) (last visit), median (Q1–Q3)	2.53 (2.06–3.52)	2.19 (1.81–2.98)	**< 0.001***
Secondary Sjögren's syndrome, *n* (%)	109 (13.3)	37 (10.3)	0.150**
Interstitial lung disease, *n* (%)	185 (34.2)	88 (33.3)	0.808**
Hypertension, *n* (%)	438 (31.9)	151 (27.5)	0.058**
Diabetes mellitus, *n* (%)	154 (11.2)	63 (11.5)	0.845**
Hyperlipidaemia, *n* (%)	215 (16.2)	93 (18.2)	0.319**
Asthma, *n* (%)	89 (6.7)	35 (6.7)	0.989**
Thyroid diseases, *n* (%)	160 (11.8)	68 (12.6)	0.622**
GIS bleeding, *n* (%)	8 (0.6)	7 (1.3)	0.148**
Cancer, *n* (%)	25 (1.8)	11 (2.1)	0.744**
Anti-TNF, *n* (%)	996 (71.8%)	299 (54.3%)	
Abatacept, *n* (%)	315 (22.7)	59 (10.7)	**< 0.001****
Rituximab *n* (%)	284 (20.5)	44 (8)	**< 0.001****
Tocilizumab, *n* (%)	207 (14.9)	31 (5.6)	**< 0.001****
Tofacitinib, *n* (%)	232 (16.7)	34 (6.2)	**< 0.001****
Methotrexate, *n* (%)	1242 (89.6)	522 (94.9)	**< 0.001****
Hydroxychloroquine, *n* (%)	1094 (78.9)	423 (76.9)	**0.330****
Leflunomide, *n* (%)	876 (63.2)	310 (56.4)	**0.005****
Sulfasalazine, *n* (%)	771 (55.6)	336 (61.1)	**0.028****

RA, rheumatoid arthritis; *GCs*, glucocorticoids; *BMI*, body mass index; *Q1–Q3*, 25th percentile–75th percentile; *RF*, rheumatoid factor; *CCP*, cyclic citrullinated peptide; *ESR*, erythrocyte sedimentation rate; *CRP*, C-reactive protein; *HAQ–DI*, Health Assessment Questionnaire–Disability Index; *CDAI*, Clinical Disease Activity Index; *SDAI*, Simplified Disease Activity Index; *PtGA*, patient global activity assessment; *VAS*, Visual Analogue Scale; *DAS-28*, Disease Activity Score-28; *GIS*, gastrointestinal; *TNF*, tumor necrosis factor

*Mann-Whitney U test

**Chi-Square test

Values with $p < 0.05$ were highlighted in bold

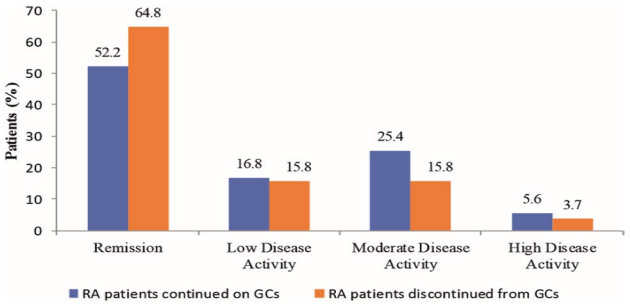

Fig. 2 Distribution of rheumatoid arthritis (RA) patients who discontinued and continued glucocorticoids (GCs) according to their disease activity at the end of the follow-up period of 59 (25–116) months ($p < 0.001$)*.*The result of 2 × 4 comparison analysis is < 0.001. The difference between the groups in the subgroup analysis is between Remission and Moderate Disease Activity Groups

discontinued 28.4% of these patients and 21.7% of the overall patient group ($n = 2{,}528$). However, 71.6% of the 1936 patients and 54.8% of the 2528 patients continued to use GCs. The ESR and CRP values, the scores of HAQ-DI, CDAI, and SDAI, and the tender and swollen joint counts before the initiation to bDMARDs or tsDMARD were similar in the patients who discontinued and continued GC therapy (Table 4). However, the PtGA-VAS and pain-VAS scores before the initiation to bDMARDs or tsDMARD were higher in the patients who continued GC therapy. The DAS-28 scores in the last visit were available in 1,045 patients; the final median DAS-28-ESR and CRP score were higher in the patients who continued GC therapy (of both $p < 0.001$). The rates of patients achieving target remission and the rates of those with low disease activity were lower in the patients who continued GC therapy (69.0% vs. 80.6%, $p < 0.001$) (Fig. 2).

Discussion

Efficacy of the combined use of GCs with a conventional DMARDs and bDMARDs or tsDMARDs in RA is well documented [1, 2]. On the other hand, international recommendations have pointed out that GCs need to be reduced and discontinued as soon as possible [2]. Reviews have indicated that long-term GC use at a dose of ≥ 5 mg/day, in particular, has numerous potential risks [16–18]. The 2019 update of EULAR recommendations on GC use in RA patients is a guide on this subject. However, data concerning to what extent these recommendations are followed in real life are limited. In the present study, we investigated the RA patients receiving bDMARDs or tsDMARD who were recorded in the TReasure registry in terms of the frequency of GC use, initial and final GC doses, and the factors associated with discontinuation of GC. In this study group including patients who had severe RA and thus had to use bDMARDs or tsDMARDs, 77% of the patients used GCs at the beginning of their treatment. While GC therapy was started in 77% of the patients in the German cohort of early arthritis (The German Course and Prognosis of Early Arthritis [CAPEA] inception cohort), this rate was observed to decrease to 64% in Latin America and even up to 48% in Canada [19–21]. In the recently published ESPOIR cohort comprising the cohort of early arthritis, GC therapy was started in 64% of the patients [22]. As the present study included relatively more severe RA patients requiring bDMARD or tsDMARD therapy, the rate of GCs use at the beginning of their treatment was within the acceptable range. The number of seropositive patients was higher, certain comorbidities (such as obesity, hyperlipidemia, hypertension) were more common, the disease activity was higher, and the use of conventional DMARDs was more common in the patients who received GCs as compared with those who did not receive GC during registration and follow-up. Likewise, in the ESPOIR cohort, seropositivity, high disease activity, and comorbidities (such as hypertension, hyperlipidemia) were more common in the group that received GCs. It is possible that in addition to patients' characteristics, prejudices of patients and physicians against GCs are the main determinant of GC use. In our study, such an inquiry (e.g. fear, anxiety) at diagnosis could not be assessed because of the observational nature of the study design.

One of the most critical warnings of the EULAR in the treatment of RA is that "low GC doses" should be preferred as the initial therapy. Nevertheless, there is no agreement on the definition of "low dose". The EULAR Task Force considered a GCs dose of ≤ 7.5 mg as a low dose [2, 13, 14]. However, in the TReasure database, it was observed that an initial GC dose of 5 mg/day was the most commonly preferred dose at a rate of 60%. Therefore, the patients were classified according to these doses. Overall, the initial GC dose was < 7.5 mg in 74% of the patients. For instance, in the German cohort, the percentage of patients who received an initial GC dose of < 7.5 mg was 20%. [19]. Accordingly, it could be suggested that the initial GC dose was able to be maintained low in our cohort. The second most critical warning of the EULAR includes "starting to reduce GCs in 3 months" and reducing the GC dose to the clinically appropriate lowest dose possible in 6 months and discontinuing if possible [2]. At the end of nearly a median follow-up period of 5 years for the RA patients registered in the TReasure database, 54.8% of the patients receiving bDMARDs or tsDMARD were still on GC therapy. This rate is far above expectations. It is observed that the GC discontinuation rate is higher particularly in RA patients achieving remission. Accordingly, this makes us think that disease control with synthetic and/or biological DMARDs used in combination with GCs have an important role in the discontinuation of

GC. On the other hand, focusing more on the study data, it was observed that nearly 18.1% of the patients were still receiving GC therapy at a dose of ≥ 7.5 mg in the last visit after the 5-year follow-up period. These are the main problematic patients among the overall RA cohort receiving bDMARDs or tsDMARDs. Regarding the characteristics of these patients, the most critical factor was the initial dose of GCs being ≥ 7.5 mg (OR 39.0). These results suggested that utmost attention should be paid while deciding the initial GC dose. As is known, approaches (perspectives) of patients and physicians toward GC-related adverse events might be quite different. The pituitary–adrenal axis is remarkably suppressed with long-term use of GCs at moderate dose [23, 24]. Along with the reduction of GC dose in such patients, weakness and fatigue become more pronounced, and possibly a more remarkable increase is observed in joint complaints [24]. Patients might resist reducing GC dose due to these effects. It is likely that "addiction to GCs" occurs when the initial GC dose exceeds 7.5 mg, which is the non-physiological dose, and thereby patients experience difficulty in stopping GCs. According to the results of the present study, in case the initial GC dose in RA is maintained at 5 mg, RA patients are more likely to be discontinued from GCs in the long term or to be continued on GC therapy within physiological doses.

The present study has some limitations. First, although initial and final GC doses of the patients were available, dose titration during the follow-up could not be evaluated. Second, thorough analyses of co-treatment with csDMARD, bDMARD, and tsDMARD that can effect steroid cessation were not possible. Thirdly, many factors may play a role in the choice of GC therapy, such as physicians' preferences, the routine of the clinic, and patients' preferences. Neither the patients nor the physicians were inquired concerning this issue in the present study, which could be considered as another limitation. Nevertheless, we think the present study has strength in that it determined the initial GC dose as the most important factor for achieving the target GC dose at the end of a 5-year follow-up period in a large cohort of RA patients.

In conclusion, the present study assessed the initial and final doses of GCs, which are frequently used in combination with synthetic or biological DMARDs, in a cohort of RA patients receiving bDMARDs or tsDMARDs. Considerably acceptable doses of GCs were observed to be used as the initial dose. However, more than half of the patients were still using GCs after the median 5-year follow-up period, which suggested the presence of certain difficulties in following the EULAR recommendations in daily practice. The most important problem is the high initial GC dose; in such a condition, achieving the target dose becomes more difficult when the non-physiological GC doses were used. Reasons for this critical relationship between the initial and final doses of GCs need to be investigated and evaluated in terms of patient/doctor perspectives.

Acknowledgements Authors are thankful to Abbvie, Amgen, Johnson and Johnson, MSD, Novartis, Pfizer, Roche, UCB

Funding Hacettepe Rheumatology Association (HRD) and Hacettepe Financial Enterprises.

Availability of data and material The datasets are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Conflict of ınterest UK received honorary from Abbvie, Amgen, Johnson and Johnson, MSD, Novartis, Pfizer, Roche, UCB. YP received honorary from Abbvie, Roche, Novartis, MSD, Pfizer. TK received honorary from Abbvie, Amgen, MSD, Novartis, Pfizer, Roche, UCB. GK received honorary from Abbvie, Amgen, Novartis, Pfizer, UCB. OK received honorary from Amgen, Johnson and Johnson, MSD, Novartis, Pfizer, Roche, UCB. ED received honorary from Abbvie, Amgen, Johnson and Johnson, MSD, Novartis, Pfizer, Roche, UCB. IE received honorary from Abbvie, Amgen, Johnson and Johnson, MSD, Novartis, Pfizer, Roche, UCB. SK received honorary from Abbvie, Amgen, MSD, Novartis, Pfizer, Roche, UCB. DE received honorary from Abbvie, Amgen, MSD, Novartis, Pfizer, UCB. CB received honorary from Abbvie, Amgen, MSD, Novartis, Pfizer, Roche, UCB. HE received honorary from Novartis, Roche. RM received honorary from Abbvie, Amgen, MSD, Novartis, Pfizer, Roche, UCB. NK received honorary from Novartis, UCB. SY received honorary from Abbvie, Amgen, Johnson and Johnson, MSD, Novartis, Pfizer, Roche, UCB. Other authors declare no conflict of interest.

Ethics approval To perform the present research, the approval for the TReasure database was obtained from the Ethics Committee of Hacettepe University in May 2017 (KA17/058) and from the Republic of Turkey Ministry of Health in October 2017 (93189304-14.03.01).

Informed consent Written informed consent of all patients was obtained.

Consent for publication Not applicable.

References

1. Singh JA, Saag KG, Louis Bridges Jr S et al (2016) 2015 American college of rheumatology guidelines for the treatment of rheumatoid arthritis. Arthritis Care Res 68:1–25. https://doi.org/10.1002/acr.22783
2. Smolen JS, Landewé R, Bijlsma J et al (2017) EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 76:960–977. https://doi.org/10.1136/annrheumdis-2016-210715
3. Tanaka Y (2013) Next stage of RA treatment: is TNF inhibitor-free remission a possible treatment goal? Ann Rheum Dis 72(Suppl 2):ii124–ii127. https://doi.org/10.1136/annrheumdis-2012-202350

4. Spivey CA, Griffith J, Kaplan C et al (2018) A Retrospective analysis of corticosteroid utilization before initiation of biologic DMARDs among patients with rheumatoid arthritis in the United States. Rheumatol Ther 5(1):255–270. https://doi.org/10.1007/s40744-017-0089-8
5. Gotzsche PC, Johansen HK (2005) Short-term low dose corticosteroids vs placebo and nonsteroidal anti-inflammatory drugs in rheumatoid arthritis. Cochrane Database Syst Rev 1:CD000189. https://doi.org/10.1002/14651858.CD000189.pub2
6. van der Veen MJ, Bijlsma JW (1993) The effect of methylprednisolone pulse therapy on methotrexate treatment of rheumatoid arthritis. Clin Rheumatol 12:500–505. https://doi.org/10.1007/BF02231779
7. Harris ED Jr, Emkey RD, Nichols JE et al (1983) Low dose prednisone therapy in rheumatoid arthritis: a double-blind study. J Rheumatol 10:713–721
8. Kirwan JR (1995) The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The arthritis and rheumatism council low-dose glucocorticoid study group. N Engl J Med 333(142):146. https://doi.org/10.1056/NEJM199507203330302
9. van Everdingen AA, Jacobs JWG, Siewertsz DR, Reesema V et al (2002) Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial. Ann Intern Med 136:1–12. https://doi.org/10.7326/0003-4819-136-1-200201010-00006
10. Black RJ, Lester S, Buchbinder R et al (2017) Factors associated with oral glucocorticoid use in patients with rheumatoid arthritis: a drug use study from a prospective national biologics registry. Arthritis Res Ther 19(1):253. https://doi.org/10.1186/s13075-017-1461-3
11. Hardy R, Cooper MS (2018) Unravelling how glucocorticoids work in rheumatoid arthritis. Nat Rev Rheumatol 14(10):566–567. https://doi.org/10.1038/s41584-018-0079-4
12. Smolen JS, Landewé RBM, Bijlsma JWJ et al (2020) EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis 79(6):685–699. https://doi.org/10.1136/annrheumdis-2019-216655
13. Smolen JS, Landewé R, Breedveld FC et al (2014) EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 73(3):492–509. https://doi.org/10.1136/annrheumdis-2013-204573
14. Kalyoncu U, Taşcılar EK, Ertenli Aİ et al (2018) Methodology of a new inflammatory arthritis registry: TReasure. Turk J Med Sci 48(4):856–861. https://doi.org/10.3906/sag-1807-200
15. Buttgereit F, da Silva JAP, Boers M et al (2002) Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. Ann Rheum Dis 61:718–722. https://doi.org/10.1136/ard.61.8.71872210.1136/ard.61.8.718
16. Ramiro S, Sepriano A, Chatzidionysiou K et al (2017) Safety of synthetic and biological DMARDs: a systematic literature review informing the 2016 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 76(6):1101–1136. https://doi.org/10.1136/annrheumdis-2016-210708
17. Nam JL, Takase-Minegishi K, Ramiro S et al (2017) Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2016 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 76(6):1113–1136. https://doi.org/10.1136/annrheumdis-2016-210713
18. Strehl C, Bijlsma JWJ, de Wit M et al (2016) Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate the implementation of existing recommendations: viewpoints from an EULAR task force. Ann Rheum Dis 75:952–957. https://doi.org/10.1136/annrheumdis-2015-208916
19. Albrecht K, Callhoff J, Schneider M et al (2015) High variability in glucocorticoid starting doses in patients with rheumatoid arthritis: observational data from an early arthritis cohort. Rheumatol Int 35:1377–1384. https://doi.org/10.1007/s00296-015-3229-x
20. Cardiel MH, Pons-Estel BA, Sacnun MP et al (2012) Treatment of early rheumatoid arthritis in a multinational inception cohort of Latin American patients: the GLADAR experience. J Clin Rheumatol 18:327–335. https://doi.org/10.1097/RHU.0b013e31826d6610
21. McKeown E, Bykerk VP, De Leon F et al (2012) Quality assurance study of the use of preventative therapies in glucocorticoid-induced osteoporosis in early inflammatory arthritis: results from the CATCH cohort. Rheumatol (Oxf) 51:1662–1669. https://doi.org/10.1093/rheumatology/kes079
22. Roubille C, Rincheval N, Dougados M et al (2017) Seven-year tolerability profile of glucocorticoids use in early rheumatoid arthritis: data from the ESPOIR cohort. Ann Rheum Dis 76(11):1797–1802. https://doi.org/10.1136/annrheumdis-2016-210135
23. Puar THK, Stikkelbroeck NMML, Smans LCCJ et al (2016) Adrenal crisis: still a deadly event in the 21st century. Am J Med 129(3):339.e1–9. https://doi.org/10.1016/j.amjmed.2015.08.021
24. Paragliola RM, Papi G, Pontecorvi A et al (2017) Treatment with synthetic glucocorticoids and the hypothalamus-pituitary-adrenal axis. Int J Mol Sci. https://doi.org/10.3390/ijms18102201

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