Biological and targeted-synthetic disease-modifying anti-rheumatic drugs with concomitant methotrexate or leflunomide in rheumatoid arthritis: real-life TReasure prospective data

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Abstract

Objective

To determine the real-life efficacy, safety, and drug-retention rates of leflunomide (LEF) or methotrexate (MTX) as a synthetic DMARD used in combination with biological DMARDs for rheumatoid arthritis (RA).

Methods

The TReasure database is a web-based, prospective, observational cohort of RA and spondyloarthritis patients from 17 centres in different regions of Turkey and data entry was enabled since December 2017. Until May 2019, 2556 RA patients on biologic treatment were recorded. Demographic and RA-related data of 1526 patient either received LEF or MTX were compared, efficacy of both drugs compared by RA-disease activity composite indices. Reasons fordrug discontinuation also recorded. Drug retention rates were compared with Kaplan-Meier curves (log-rank test).

Results

Of 2556 RA patients 1526 (59.7%) were receiving concomitant LEF (n=646, 42.3%; median follow up 35 months) or concomitant MTX (n=880, 57.3%; median follow-up 32 months) at the time of initiation to their first bDMARDs. The LEF group were older and had longer disease duration, proportion of females and seropositive patients was higher in this group. In the LEF group, non-anti-TNF agents were used in higher rate. Remission rates, changes in composite indices and rate of comorbidities and adverse events were similar in both groups. The retention rate of LEF + non-anti-TNF b/tsDMARDs was higher compared to MTX + anti–TNF bDMARDs (p=0.002, log-rank). Rates of adverse events were similar in both groups.

Conclusion

LEF in combination with either anti-TNF or non-anti-TNF drugs appears as an effective and safe therapeutic option at least as MTX.

Key words

leflunomide, methotrexate, rheumatoid arthritis, biologic or targeted-synthetic DMARDs

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Received on March 28, 2020; accepted in revised form on July 27, 2020.

Funding: this study was funding by Hacettepe Rheumatology Society.

Competing interests: see page 858.

Introduction

Biological and targeted-synthetic disease-modifying anti-rheumatic drugs (DMARDs) used for the treatment of patients with rheumatoid arthritis (RA) have led to revolutionary changes in rheumatology practice. In biological databases, the rate of patients receiving with biological DMARDs (bDMARDs) monotherapy ranges from 10–30% (1, 2). Accordingly, a substantial proportion of the patients are receiving a bDMARD with a concomitant synthetic DMARD. The European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) recommend methotrexate (MTX) as the main synthetic DMARD to be used in combination with biological DMARDs. Although MTX is the main synthetic DMARD used in combination with biological DMARDs in RA studies, intolerance to MTX can develop in years along with its long-term use (3). Moreover, leflunomide (LEF) is another anchor synthetic DMARD for the management of RA (4, 5).

Randomised controlled trials (RCTs) take short-term use of synthetic DMARDs into account. In addition, MTX-related adverse events (AEs) in RA patients would increase cumulatively in years and drug intolerance may develop with its long-term use (3). However, such an observation can be verified only using real-life data. Accordingly, the TReasure database was introduced into use in December 2017 with the participation of 17 centres. In this database, MTX is one of the anchor synthetic DMARDs in the treatment of RA and LEF is the other one. Therefore, the TReasure database is an appropriate database to evaluate the potential effects and AEs of LEF when used as a concomitant synthetic DMARD.

The aim of the present study was to determine the efficacy, safety, and drug-retention rates of LEF or MTX as a synthetic DMARD used in combination with biological DMARDs.

Methods

TReasure database and patient selection

The TReasure database is a web–based, prospective, observational cohort of RA and spondyloarthritis (SpA) patients from 17 centres in different regions of Turkey (6). The database was established in 2017 and data entry by the centres was started in December 2017. As of May 2019, data entry was completed for a total of 7,198 patients receiving bDMARDs, of whom 2,556 had RA, 4,264 had SpA, and 378 had psoriatic arthritis.

The starting date of bDMARDs in RA patients was determined as the "*date of study enrolment*". The study included the patients who were receiving LEF or MTX while using their first biological DMARDs. Patients who received LEF or MTX before the date of study enrolment but who discontinued the treatment due to inefficacy and/or AEs were excluded from the analyses.

Demographic and clinical characteristics and measurements

Each patient was diagnosed by his/her treating physician. Patients' data regarding age, gender, disease duration, and rheumatoid factor and anti-cyclic citrullinated peptide (CCP) antibody positivity were recorded. Smoking status, body mass index, and comorbidities were also recorded. The following disease activity parameters were recorded at the time of initiation to first biological DMARD: erythrocyte sedimentation rate (mm/h), C-reactive protein (CRP; mg/L), swollen (66) and tender (68) joints count, the Health Assessment Questionnaire-Disability Index (HAQ-DI) scores, and pain-Visual Analogue Scale (VAS, 0–100 mm), fatigue-VAS (0–100 mm), and the patients' global disease activity assessment (PtGA)-VAS (0–100 mm) scores. 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 bDMARDs and targeted synthetic DMARDs included in the TReasure database were as follows: anti-tumour necrosis factor (TNF) alpha drugs (adalimumab, infliximab, golimumab, certolizumab or etanercept), non-TNF alpha biological DMARDs (abatacept, rituximab, and tocilizumab), and targeted synthetic DMARDs (tofacitinib).

Table I. Demographic characteristics of the patients receiving biological disease-modifying anti-rheumatic drugs (bDMARDs) with concomitant leflunomide or methotrexate and disease activity of these patients before the use of bDMARDs.

	Biological DMARD + Leflunomide n=646	Biological DMARD + Methotrexate n=880	*p*-value
Female sex, %	534 (82.7)	687 (78.1)	**0.027**
Age, year, median (Q1–Q3)	57 (49–65)	54 (41–62)	**<0.001**
Disease duration, year, median (Q1–Q3)	12 (7–19)	9 (5–14)	**<0.001**
BMI, median (Q1–Q3)	28.6 (24.6–32.5)	28.2 (24.4–33.1)	0.711
RF positive, n/N (%)	444/617 (72)	521/827 (63)	**<0.001**
Anti-CCP positive, n/N (%)	287/441 (65.1)	369/648 (56.9)	**0.007**
RF or anti-CCP positive, n/N (%)	487/627 (77.7)	582/842 (69.1)	**<0.001**
ESR, mm/h, median (Q1–Q3)	35 (19–52)	30 (16–50)	**0.043**
CRP mg/lt, median (Q1–Q3)	15.4 (6.71–32.9)	14.9 (5.66–37.9)	0.553
Anti-TNF, n (%)	372 (57.6)	567 (64.5)	**<0.001**
Rituximab	99 (15.3)	65 (7.4)	
Abatacept	108 (16.7)	135 (15.4)	
Tocilizumab	28 (4.3)	35 (4)	
Tofacitinib	39 (6.0)	77 (8.8)	
Non-anti-TNF, n (%)	274 (42.4)	312 (35.5)	
Dose (MTX or LEF), median (min-max)	20 (10-40)	15 (2.5-25)	
Total csDMARD count, median (min-max)	2 (1-3)	2 (1-3)	0.36
Hydroxychloroquine, n/N (%)	346/646 (53.6)	431/880 (49.0)	0.077
Sulfasalazine, n/N (%)	76/646 (11.8)	121/880 (13.8)	0.253
Number of swollen joints, median (Q1–Q3)	3 (1–5)	3 (2–5)	0.343
Number of tender joints, median (Q1–Q3)	7 (3–11)	6 (3–10)	0.576
PtGA-VAS, median (Q1–Q3)	70 (50–80)	70 (50–80)	0.744
Pain-VAS, median (Q1–Q3)	60 (50–80)	70 (50–80)	0.371
Fatigue-VAS, median (Q1–Q3)	70 (50–80)	70 (50–80)	0.367
HAQ-DI Score, median (Q1–Q3)	0.95 (0.55–1.4)	0.95 (0.55–1.4)	0.974
CDAI score, median (Q1–Q3)	21.8 (12–33)	18.5 (12–30)	0.601
SDAI score, median (Q1–Q3)	43 (23.65–65.05)	39.65 (21.9–60)	0.370

DMARD: disease-modifying anti-rheumatic drug; Q1–Q3: 25th percentile-75th percentile; BMI, body mass index; RF: rheumatoid factor; CCP: anti-cyclic citrullinated peptide; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TNF: tumour necrosis factor; PtGA: patient global activity assessment; VAS: visual analogue scale; HAQ-DI: Health Assessment Questionnaire-Disability Index; CDAI: Clinical Disease Activity Index; SDAI: Simplified Disease Activity Index.

Treatment response and medication continuation

Patients included in the TReasure database have been followed up observationally. In the present study, patients' data were recorded prospectively between December 2017 and May 2019 and retrospectively before December 2017. The last control visits of the patients were recorded and the disease activity was assessed based on the patients' condition in the last visit. The DAS-28 scores were calculated to determine their disease activity. According to the DAS-28 scores, patients were classified as those in remission (a DAS-28 score of <2.6), those with low disease activity (a DAS-28 score of 2.6–3.2), those with moderate disease activity (a DAS-28 score of >3.2–5.1), and those with high disease activity (a DAS-28 score of >5.1) (7). In patients receiving a biological DMARD with concomitant LEF or MTX, if the concomitant drug was discontinued, the date of and the reasons for discontinuation were recorded.

Statistical analysis

Data analyses were performed using the Predictive Analytics SoftWare (PASW) 18.0 (SPSS Inc., Chicago, IL, USA) for Windows. Descriptive statistics were expressed as number and percentages for categorical variables and as median, 25th and 75th percentile (Q1 and Q3) for numerical variables. When chi-square condition was met, chi-square test was used for two group comparisons and multiple comparisons; however, when chi-square condition was not met, Fisher's exact test was used for two group comparisons. Mann-Whitney U-test was used for comparison of non-normally distributed variables. The Kaplan-Meier survival analysis was used to calculate the retention rates of LEF and MTX; for comparison of LEF and MTX retention rates, log-rank test was used. A *p*-value of <0.05 was considered statistically significant.

Ethical approval

The present study was approved by the Local Ethics Committee of Hacettepe University in May 2017 (KA-17/058) and by the Republic of Turkey Ministry of Health in October 2017 (93189304-14.03.01). Written informed consent was obtained from all patients.

Results

Demographical and clinical findings

Of 2556 RA patients recorded in the TReasure database, 1526 (59.7%) were receiving concomitant LEF (n=646, 42.3%) or concomitant MTX (n=880; 57.3%) at the time of initiation to their first bDMARDs; these patients were included in the analyses. The patients receiving an advanced DMARD with concomitant LEF were older and had longer disease duration, rate of females and the number of seropositive patients was higher in this group (Table I). While anti-TNF therapies were mostly preferred as bDMARDs in the patients

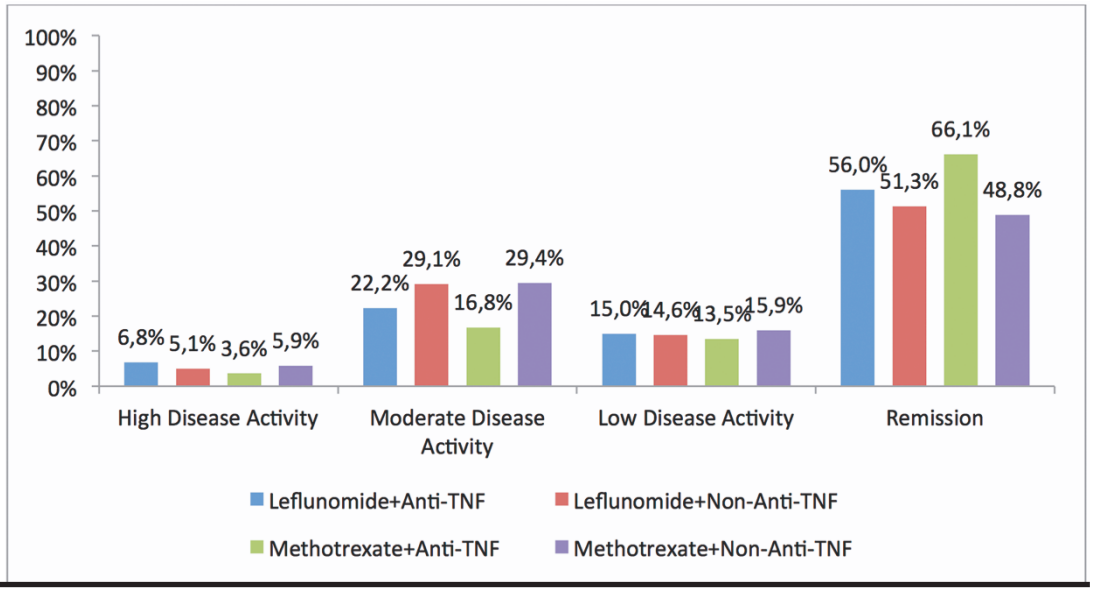

Fig. 1. Distribution of the patients receiving biological disease-modifying anti-rheumatic drugs (bDMARDs) with concomitant LEF or MTX according to their disease activity. TNF: tumour necrosis factor.

receiving MTX, non-anti-TNF bDMARDs were mostly preferred in those receiving LEF (Table I). Hypertension (42.6% *vs*. 24.0%, $p<0.001$), hyperlipidaemia (22.0% *vs*. 12.6%, $p<0.001$), and asthma (8.4% *vs*. 5.0%, $p=0.007$) were significantly more common in the patients receiving concomitant LEF. The frequencies of other comorbidities were similar in the patients receiving concomitant LEF or MTX; the distribution of the rates of comorbidities in the patients receiving concomitant LEF was as follows: 13.3% for diabetes mellitus, 2.3% for chronic obstructive pulmonary disease (COPD), 12.3%, for thyroid diseases, 2.1% for cancer, and 0.6 % for cerebrovascular event).

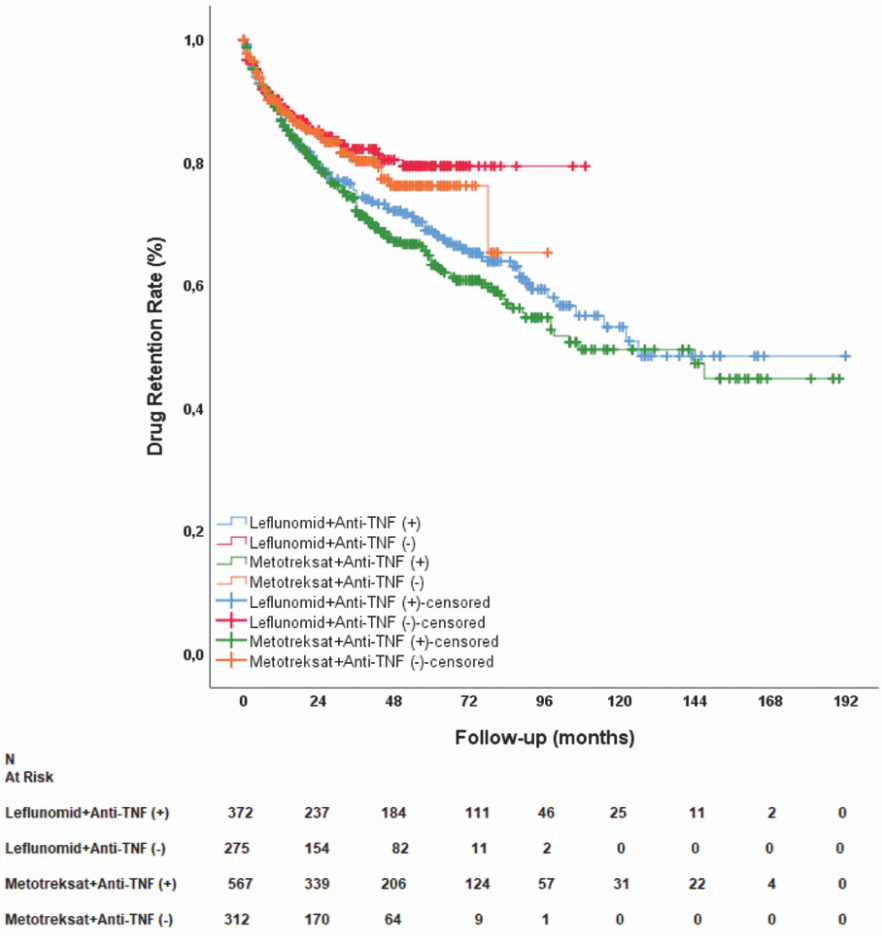

Fig. 2. Retention rates of concomitant leflunomide or methotrexate. TNF: tumour necrosis factor.

Response to treatment with bDMARDs with concomitant LEF or MTX

The median duration of follow-up was 35 months (Q1–Q3, 12–64 months) for the patients receiving bDMARDs with concomitant LEF and 32 months (Q1–Q3, 14–56 months) for the patients receiving bDMARDs with concomitant MTX. The last control DAS-28 scores of the patients according to MTX or LEF usage as a synthetic DMARD and anti-TNF or non-anti-TNF usage as a bDMARD are shown in Figure 1. Accordingly, the rate of patients achieving remission was 54.7% with concomitant use of LEF and bDMARDs and 59.3% with concomitant use of MTX and bDMARDs. The rate of patients achieving remission was similar when LEF was combined with an anti-TNF bDMARD or with a non-anti-TNF bDMARD (56.0% and 51.3%, respectively; $p=0.365$). On the other hand, better remission rates were obtained with concomitant use of MTX with an anti-TNF agent as compared with its concomitant use with a non-anti-TNF agent (66.1% and 48.8%, respectively, $p<0.001$).

Table II. Retention rates of concomitant leflunomide or methotrexate.

	12th month	24th month	36th month	48th month	60th month	72th month	96th month
Leflunomide + biological DMARD	89.9	82.2	78.2	75.3	72.6	69.9	63.2
Leflunomide + anti–TNF	89.4	80.0	75.5	72.1	69.0	65.9	59.3
Leflunomide + non–anti-TNF	90.3	85.3	82.2	80.4	79.4	79.4	---
Methotrexate + biological DMARD	88.8	81.6	76.3	70.3	67.9	64.1	57.4
Methotrexate + anti-TNF	86.0	80.1	74.2	67.7	64.9	60.8	54.8
Methotrexate + non-anti-TNF	90.3	84.9	80.9	76.2	76.2	76.2	65.3

Comparing with the baseline values at the time of initiation to first bDMARD, the percent (%) change in the pain-VAS scores (-37.5 [-62.5–0] *vs*. -42.86 (-63.64 – -11.11), p=0.021], the percent (%) change in the PtGA-VAS scores (-25 [-57.14–0) *vs*. -37.5 [-66.67–0], p=0.034) and the percent (%) change in HAQ-DI scores (-40 [-76.92–5) *vs*. -47.72 [-83.77– -4.42], p=0.002) were better in the patients receiving concomitant MTX. Moreover, the changes in the DAS-28 scores (-33.28 [-52.3 – -5.08] *vs*. -36.83 [-51.98 – -9.34], p=0.47), the changes in the CDAI scores (-65.71 [-74.19 – -29.27) *vs*. -64.9 [-79.31 – -11.43], p=0.082), and the changes in the SDAI scores (-61.7 [-76.36 – -0.82] *vs*. -65.49 [-76.74 – -10.92], p=0.46) were similar in the patients receiving concomitant MTX and LEF.

Retention rates of concomitant synthetic DMARDs (LEF and MTX)

The Kaplan-Meier curve for retention rates of LEF and MTX combined with the first bDMARDs are shown in Figure 2 and the retention rates are summarised in Table II. Accordingly, a significant difference was determined between the retention rates of concomitant synthetic DMARDs (log–rank test, p=0.007). The retention rate of LEF or MTX was higher when combined with non-anti-TNF bDMARDs. Subgroup analysis revealed that as compared with the concomitant use of LEF with anti-TNF bDMARDs, the retention rate of LEF was higher when it was combined with non-anti-TNF bDMARDs (p=0.025). Similarly, the retention rate of MTX was also higher when combined with non-anti-TNF bDMARDs as compared with its concomitant use with anti–TNF bDMARDs p=0.021). The most striking difference between the groups was observed when LEF was combined with non-anti-TNF bDMARDs and MTX was combined with anti-TNF bDMARDs (p=0.002).

During the follow-up period, LEF was discontinued in 160 (24.8%) patients and MTX was discontinued in 241 (27.4%) patients. The reasons for discontinuation of LEF and MTX were inefficacy in 29 (1.9%) patients, AEs in 100 (6.6%) patients, doctor's/patient's decision in 98 (6.4%) patients, pregnancy in 11 (0.7%) patients, other in 14 (0.9%) patients, and unknown in 163 (10.7%) patients. The reasons for discontinuation of LEF were inefficacy in 6 (0.9%) patients, AEs in 38 (5.9%) patients, doctor's/patient's demand in 41 (6.3%) patients, pregnancy in 3 (0.5%) patients, other in 5 (0.8%) patients, and unknown in 69 (10.7%) patients. The reasons for discontinuation of MTX were inefficacy in 23 (2.6%) patients, AEs in 62 (7.0%) patients, doctor's/patient's demand in 57 (6.5%) patients, pregnancy in 8 (0.9%) patients, other in 9 (1.0%) patients, and unknown in 94 (10.7%) patients.

Discussion

Methotrexate is the first synthetic DMARD recommended by both the EULAR and the ACR to be used in combination with biological DMARDs (8, 9). MTX has been frequently studied in the RCTs and in their extended arms (11-15). On the other hand, it is known that MTX, in real-life, is discontinued in years for various reasons. In the RABBIT registry, it was reported that concomitant MTX was discontinued within 36 months in 17% of the patients receiving MTX in combination with an anti-TNF agent (16). For this reason, the need for another synthetic DMARD as an alternative to MTX may arise in a substantial proportion of patients. Both the EULAR and the ACR have stated that LEF or sulfasalazine can be used instead of MTX when necessary, and their safety data regarding infections causing hospitalisation were similar when combined with bDMARDs with a slightly lower incidence in patients receiving MTX (8-10). In the present study, we evaluated the efficacy, safety, and retention rate of concomitant use of MTX or LEF using the TReasure real-life data. Indeed, the discontinuation rates were 21.8% and 23.7% for the concomitant LEF and MTX, respectively, in the 36th month. Interestingly, the retention rates of LEF were significantly better when combined with non-anti-TNF bDMARDs; for instance, while the retention rate in the 72nd month was 79.4% in the patients receiving a non-anti-TNF bDMARD with concomitant LEF, it was 60.8% in the patients receiving an anti-TNF bDMARD with concomitant MTX. These results indicated that concomitant use of LEF particularly with non-anti-TNF bDMARDs in real life led to a difference in terms of dug retention.

Until today, concomitant use of LEF or MTX has been evaluated several times in RA registries. For instance, the DREAM, BSRBR, RABBIT, and SCQM registries provided data on the use of LEF or MTX in combination with bDMARDs (16-19). In these registries, only anti-TNFs were selected as bDMARDs. On the other hand, the TReasure registry provided the results of all bDMARDs used in real life. Hence, in our data, non-anti-TNF drugs accounted for 42% of bDMARDs used in combination with LEF. From this point of view, the TReasure database provides specific results reflecting the real life. Observational studies about the availability of LEF in combination with non-anti-TNF bDMARDs are quite limited in number. A small observational study

from Spain compared LEF (n=26) and MTX (n=55) for combination treatment with tocilizumab and reported no difference in terms of efficacy and safety (20). A *post-hoc* analysis of the RCTs (ATTAIN, ASSURE, and ARRIVE) in which abatacept was used in combination with synthetic DMARDs was published. Accordingly, no difference was determined between the concomitant uses of MTX and LEF with abatacept in terms of efficacy and safety (21). Comparative studies about the use of MTX or LEF in combination with tofacitinib are lacking. The use of LEF or MTX in combination with rituximab was evaluated in the CERERRA trial conducted in Europe with the participation of 10 different countries. In the CERERRA trial comprising 2265 patients, 1195 patients received rituximab and MTX, 177 patients received rituximab and LEF, and 505 patients received rituximab monotherapy (22). Interestingly, better EULAR response was reported in whom receiving rituximab and LEF; however, no difference was determined in terms of safety. Likewise, in the TReasure database, anti-TNF use was lower and non-anti-TNF bDMARD use was higher in the LEF arm (58% *vs*. 65%). However, this difference appeared to be associated mainly with the frequent use of rituximab in the LEF arm (15% *vs*. 7%); other bDMARDs (tocilizumab, abatacept, and tofacitinib) were used in similar rates. The frequent concomitant use of rituximab and LEF in the present study could be considered the signal of synergistic effect.

There is no consensus on the data obtained from the DREAM, BSRBR, RABBIT, and SCQM registries. For instance, the results of SCQM system demonstrated no difference between MTX and LEF use in combination with anti-TNF drugs, whereas BSRBR and DREAM registries reported concomitant MTX to be superior. In the RABBIT registry, although the combination of anti-TNF and LEF had slightly lower efficacy than the combination of anti-TNF and MTX, most of the patients receiving LEF in combination with anti-TNF previously received MTX as was mentioned by the authors, and thereby higher treatment response rates was already an expected result. Taking all bDMARDs into account, the results of the TReasure database revealed that concomitant use of MTX was slightly better than concomitant use of LEF in terms of achieving remission (54.7% *vs*. 59.3%). However, taking only the patients receiving anti-TNF into account, remission was more frequently achieved in those using MTX than in those using LEF (66.1% *vs*. 56.0%). These results were consistent with the findings of the DREAM, BSRBR, and RABBIT registries. There was no difference between concomitant uses of MTX and LEF with non-anti-TNF drugs in terms of retention rates; however, as compared with anti-TNF biological DMARDs, the remission rates were observed to be significantly reduced when used in combination with non-anti-TNF biological DMARDs.

The effects of concomitant MTX or LEF on the retention rates of bDMARDs were demonstrated in all of the 4 biological registries. While they had similar effects on the retention rate of anti-TNFs in the SCQM registry, the DREAM and BSRBR registries emphasised that the use of anti-TNFs with concomitant MTX had more favourable effects than the use of anti-TNFs with concomitant LEF on the retention rates of bDMARDs. The TReasure database was established in 2017 with the participation of 17 centres and the data of patients followed in the relevant centres were recorded within a 20-month period. Thus, the patients who continued to receive bDMARD therapy were recorded. For this reason, the effects of concomitant use of MTX or LEF on retention rates of bDMARDs could not be investigated; instead, retention rate of MTX or LEF used in combination with bDMARDs were separately given. Such an assessment is available only in the RABBIT registry among the 4 registries mentioned above. In the RABBIT registry, the retention rate of MTX was found to be better than that of LEF. In the TReasure database, no difference was determined between retention rates of concomitant MTX and LEF in the patients receiving anti-TNF agents. Nevertheless, regarding non-anti-TNF drugs, LEF became prominent as a synthetic drug in terms of retention rates.

Differences in several clinical characteristics of the patients receiving concomitant LEF attracted attention in the TReasure database. Firstly, seropositivity was higher in this patient group. In this respect, among the above-mentioned registries, a similar signal was observed only in the DREAM database (anti-TNF+LEF *vs*. anti–TNF+MTX: 77.9% *vs*. 70.7%). Another difference was older age of the patients receiving LEF. Although such a difference was not observed in the above-mentioned registries, a real-life data from France revealed that as compared with MTX, LEF was preferred in older patients (23).

In the present study, the time of initiation to a bDMARD was accepted as the baseline, which was a limitation of the present study. Data from that period were not included in the analysis as they are retrospective. Patients might have used various synthetic DMARDs and glucocorticoids before that time, which appears as a confounding factor, especially for the patients who used MTX and then switched to LEF before the initiation of bDMARD. This situation may also be the cause of channelling bias which may explain the better retention of non-TNF bDMARD combination of LEF as this combination is generally used later in the disease course and they considered as the later steps of treatment course. Another limitation of this study was the lacking of the structured assessment of functional status and structural remission.

In conclusion, synthetic DMARDs are frequently used together with bDMARDs for the treatment of RA patients in real life. Although MTX is the synthetic DMARD firstly recommended for this purpose, it is discontinued or cannot be used due to loss of efficacy or AEs within years. In such cases, LEF in combination with either anti-TNF or non-anti-TNF drugs seems to have similar efficacy and safety profile to MTX. There is limited data on the use of LEF particularly in combination with non-anti-TNF bDMARDs. In this respect, the TReasure database has additional contributions to the literature.

Acknowledgments

Collaborators

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Competing interests

G. Kimyon has received honoraria from Abbvie, Amgen, Novartis, Pfizer, UCB; U. Kalyoncu has received honoraria from Abbvie, Amgen, Johnson and Johnson, MSD, Novartis, Pfizer, Roche, UCB); S. Kiraz from Abbvie, Amgen, Johnson and Johnson, MSD, Novartis, Pfizer, Roche, UCB; C. Bes from Abbvie, Amgen, MSD, Novartis, Pfizer, Roche, UCB; O. Kucuksahin from Amgen, Johnson and Johnson, MSD, Novartis, Pfizer, Roche, UCB; N. Kanitez from Novartis, UCB; A. Erden from Amgen, Novartis, Roche, UCB; L. Kilic from Abbvie, Amgen, MSD, Novartis, Pfizer, Roche, UCB; T. Kasifoglu from Abbvie, Amgen, MSD, Novartis, Pfizer, Roche, UCB; H. Emmungil from Novartis, Roche; S.S. Koca from Abbvie, MSD, Novartis, Pfizer, Roche, UCB; S. Akar from Abbvie, Amgen, MSD, Novartis, Pfizer, Roche, UCB; M. Cinar from Abbvie, Amgen, MSD, Novartis, Pfizer, Roche, UCB; V. Yazisiz from Abbvie, Actelion, Amgen, MSD, Novartis, Pfizer, Roche, UCB; D. Ersozlu from Abbvie, Amgen, MSD, Novartis, Pfizer, UCB; R. Mercan from Abbvie, Amgen, MSD, Novartis, Pfizer, Roche, UCB; I. Ertenli from Abbvie, Amgen, Johnson and Johnson, MSD, Novartis, Pfizer, Roche, UCB; the other co-authors have declared no competing interests.

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