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Safety of the Methotrexate–leflunomide Combination in Rheumatoid Arthritis: Results of a Multicentric, Registry-based, Cohort Study (BiobadaBrasil)

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ABSTRACT. ***Objective.*** To evaluate the safety of the methotrexate (MTX)–leflunomide (LEF) combination in rheumatoid arthritis (RA), comparing it with other therapeutic schemes involving conventional synthetic (cs-) and biologic (b-) disease-modifying antirheumatic drugs (DMARDs) or Janus kinase inhibitors (JAKi).

Methods. Patients with RA starting a treatment course with a csDMARD (without previous use of bDMARD or JAKi) or their first bDMARD/JAKi were followed up in a registry-based, multicentric cohort study in Brazil (BiobadaBrasil). The primary outcome was the incidence of serious adverse events (SAEs); secondary outcomes included serious infections. Multivariate Cox proportional hazards models and propensity score matching analysis (PSMA) were used for statistical comparisons.

Results. In total, 1671 patients (5349 patient-years [PY]) were enrolled; 452 patients (1537 PY) received MTX + LEF. The overall incidence of SAEs was 5.6 per 100 PY. The hazard of SAEs for MTX + LEF was not higher than for MTX or LEF (adjusted HR [aHR] 1.00, 95% CI 0.76–1.31, $P = 0.98$). MTX + LEF presented a lower hazard of SAEs (aHR 0.56, 95% CI 0.36–0.88, $P = 0.01$) and infectious SAEs (aHR 0.48, 95% CI 0.25–0.94, $P = 0.03$) than bDMARDs/JAKi with MTX or LEF. MTX + LEF presented lower hazard of SAEs than MTX + sulfasalazine (SSZ; aHR 0.33, 95% CI 0.16–0.65, $P = 0.002$). Analysis using PSMA confirmed the results obtained with traditional multivariate Cox analysis.

Conclusion. In our study, MTX + LEF presented a relatively good overall safety profile in comparison to MTX + SSZ and schemes involving advanced therapies in RA.

Key Indexing Terms: antirheumatic drugs, biologics, drug safety, leflunomide, methotrexate, rheumatoid arthritis

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The use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), especially methotrexate (MTX), is the first step in the treatment of rheumatoid arthritis (RA). After failure of MTX monotherapy, it is possible to step up treatment using combinations of csDMARDs,[1,2,3] usually adding sulfasalazine (SSZ) and/or hydroxychloroquine (HCQ) to oral or injectable MTX. Triple therapy (MTX-SSZ-HCQ combination) has demonstrated similar efficacy in comparison to the combination of MTX and biologic DMARDs (bDMARDs) in randomized controlled trials (RCTs).[4,5] However, previous evidence has questioned the effectiveness of triple therapy in RA,[6,7,8] mainly because of the relatively poor tolerability of SSZ.[6,7] A possible alternative to triple therapy is the association of MTX and leflunomide (LEF; MTX + LEF), which has shown higher efficacy than monotherapy with MTX[9] and similar efficacy compared to MTX + rituximab (RTX).[10] However, the MTX-LEF combination has not gained ample acceptance in Europe and North America, mainly due to evidence suggesting higher risk of hepatic[11,12] and/or hematologic adverse effects.[13] Conversely, Cannon, *et al*,[14] in a large retrospective cohort study, observed no increased incidence of adverse events (AEs) with MTX + LEF in comparison to other schemes of csDMARDs. Other studies on MTX + LEF presented generally small sample sizes,[11,15–27] and no previous study has compared the safety of this combination with that of treatment regimens involving bDMARDs or Janus kinase inhibitors (JAKis). Considering this, in the present study, our aim was to assess the safety of MTX + LEF in a registry-based cohort of patients with RA, comparing it with other therapeutic schemes including csDMARDs and advanced therapies for RA.

METHODS

BiobadaBrasil is a multicentric, observational, longitudinal study following up patients with rheumatic diseases. BiobadaBrasil, which is part of Biobadamerica, is meant to monitor the safety of bDMARDs (and more recently, JAKis), but patients starting treatment with a csDMARD are allowed to be included as a control group.[28] It is sponsored by the Brazilian Society of Rheumatology (BSR),[29,30] and involves 32 public and private rheumatology centers from most Brazilian states.[28] The main investigators of each center are required to be rheumatology specialists certified by the BSR. The study was approved by the research ethics committee of the Hospital das Clínicas da Universidade Federal do Paraná (approval number 17 41 158/2008-08) and all other participating centers before inclusion of the first patient; all patients signed written informed consent.[29] The study was performed in compliance with the principles of the Declaration of Helsinki.

Patients. For the present study, we exclusively selected patients with RA according to 1987 American College of Rheumatology (ACR) criteria[31] or the 2010 European League Against Rheumatism/ACR criteria,[32] who were starting a new csDMARD (SSZ, antimalarials, cyclosporine, MTX, or LEF, and had no previous exposure to bDMARDs) or their first bDMARD or JAKi.[33] The inclusion of patients in BiobadaBrasil was not necessarily consecutive and was made according to the availability of each study site. The exclusion criterion were overlapping with other connective tissue diseases, except for secondary Sjögren syndrome. Recruitment of patients to BiobadaBrasil started on January 1, 2009.[28] Only patients starting a treatment course on or after this date were included in the present analysis. Patients could be registered in the cohort up to 6 months from treatment initiation. Patients with a time gap between starting a treatment course and registration should have been closely followed and have complete records of clinical and demographic features, therapeutic scheme, and AEs during that period.[33] After patients' inclusion, all new data were collected prospectively, characterizing this study as ambispective.

Study factors. Our main objective was to evaluate the safety of MTX + LEF in the treatment of RA in comparison to other schemes. Initially, we compared the hazard of AEs of MTX + LEF and a control group using either MTX or LEF (not in combination with each other). Next, we compared patients using MTX + LEF with those receiving bDMARDs or JAKis along with MTX or LEF. Analysis was also performed comparing MTX + LEF with MTX and with MTX + bDMARDs/JAKis. As a secondary goal, we compared the hazards of AEs of MTX + LEF with those of the combination of MTX and SSZ (MTX + SSZ). In an exploratory analysis, we compared patients receiving bDMARDs/JAKis (with MTX or LEF) with those receiving bDMARDs/JAKis with MTX + LEF. Confounding variables (recorded at baseline) considered here were Disease Activity Score in 28 joints; sex; age; seropositivity (for rheumatoid factor and/or anticyclic citrullinated peptide); disease duration; smoking; diabetes; hypertension; renal failure; ischemic cardiomyopathy; heart failure; history of cancer; chronic obstructive pulmonary disease; concurrent use of bDMARDs/JAKis, SSZ, antimalarials (HCQ or chloroquine), and corticosteroids; starting year; hypercholesterolemia; osteoporosis; and hepatitis B and C. Study center was also included as an independent variable in some sensitivity analyses and in all propensity score matching analyses (PSMA).

Outcomes. Information recorded in BiobadaBrasil originated from the clinical records of visits at each rheumatology center. Each of the centers has its own record system. In case of an AE, a local investigator completed a common Web-based platform, actively looking for a list of AEs based on Medical Dictionary for Drug Regulatory Activities nomenclature.[34] Data collection and a record in the databank occurred whenever AEs were detected during regular or unscheduled visits, or when a change in treatment regimen occurred. Relevant AEs were collected both spontaneously and by active physician interrogation about common side effects, as well as by assessment of medical exams and/or review of medical reports. The frequency and interval between the evaluation of laboratory tests was determined by each center, but generally followed current recommendations for drug monitoring.[1] There was no prespecified threshold of laboratory abnormalities above/below which the report of an AE was mandatory. Definitions of severity and outcomes of AEs were stated in the BiobadaBrasil protocol.[29] A serious AE (SAE) required immediate notification and was defined as a condition that caused death or was life threatening, led to inpatient hospitalization or prolongation of an existing one, or caused important or persistent disability or a congenital abnormality/birth defect. Pregnancy was included among SAEs.[29]

In the present study, the primary outcome was the incidence of SAEs of any kind. Secondary outcomes were fatal AEs and total (any) AEs, serious and total infections, cardiovascular (CV; including stroke), hepatic, hematologic, respiratory tract, and gastrointestinal AEs. Supplementary Table 1 (available with the online version of this article) describes the codification for each type of AE. Secondary outcomes of special interest were anemia, neutropenia (including pancytopenia), and elevation of hepatic transaminases. Interruption of treatment due to any

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reason (including those lost to follow-up; except pregnancy or disease remission), inefficacy, and AE or death also served as secondary outcomes (Supplementary Table 2).

Details of data management and quality control are described in Supplementary Text 1 (available with the online version of this article). For the present analysis, only the first course of treatment, after patients' inclusion in the cohort, was considered for analysis. A treatment course was defined as a period during which the medication scheme did not change, except for dose adjustments. Follow-up was interrupted at moment of the first event. Patients not presenting outcomes during the course of therapy were censored 90 days after treatment interruption, on the day before the start of a new treatment course, at the moment of death or loss to follow-up, or on November 19, 2019 (whichever came first).

Statistical analysis. The data were analyzed using SPSS for Windows, version 20.0 (IBM Corp.), and the Survival, MatchIt, and Stddiff packages of R (version 3.3.3, R Foundation for Statistical Computing). The association between categorical variables was tested using Pearson chi-square or Fisher exact test. Variables with a normal distribution were presented as mean and SD, and the between-group comparisons were performed using *t* test or ANOVA. Nonnormal quantitative variables were presented as the median and IQR, and between-group comparisons were performed using the Mann-Whitney *U* test or Kruskal-Wallis test. Incidence-density data (along with 95% CIs) were estimated for most outcomes. Survival analysis was performed with Kaplan-Meier curves and uni- and multivariate Cox proportional hazards models. Sensitivity and subgroup analyses were planned to account for possible sources of bias. Results for the primary outcome were confirmed using PSMA.[35,36,37] *P* values ≤ 0.05 were considered statistically significant (all presented *P* values are 2-tailed). See further details in Supplementary Text 2 (available with the online version of this article).

RESULTS

Description of the sample. Of 2111 patients, 1671 (5348.7 patient-years [PY]) starting follow-up on January 1, 2009, or thereafter, were included in the analysis (Figure 1). Clinical and demographic characteristics of these patients, divided according to the use of MTX and LEF, are described in Table 1. In general, patients receiving treatment with MTX + LEF were more frequently seronegative, more commonly using corticosteroids, and less frequently using SSZ and biologic agents than other groups of patients. Only 2 patients received treatment with cyclosporine (both in the group receiving neither MTX nor LEF). Patients using JAKis were taking tofacitinib exclusively. The median duration of follow-up in the entire sample was 2.17 years (IQR 0.96–4.59 yrs) before censoring or the first SAE. The overall incidence of SAEs (298 in total) was 5.6 per 100 PY. Most SAEs (220/298, 73.8%) were observed after 6 months of follow-up. Total follow-up of patients on MTX + LEF was 1536.6 PY.

Comparison of MTX + LEF with MTX/LEF. The comparison of the incidences and hazards of primary and secondary outcomes between MTX + LEF and a category representing use of MTX or LEF is depicted in Table 2. There was no significant increase in the hazard of SAEs, but total AEs presented higher incidence with MTX + LEF in relation to therapy with MTX or LEF. Total CV (univariate analysis) and total infectious events (multivariate analysis) were also more frequent with MTX + LEF. In the

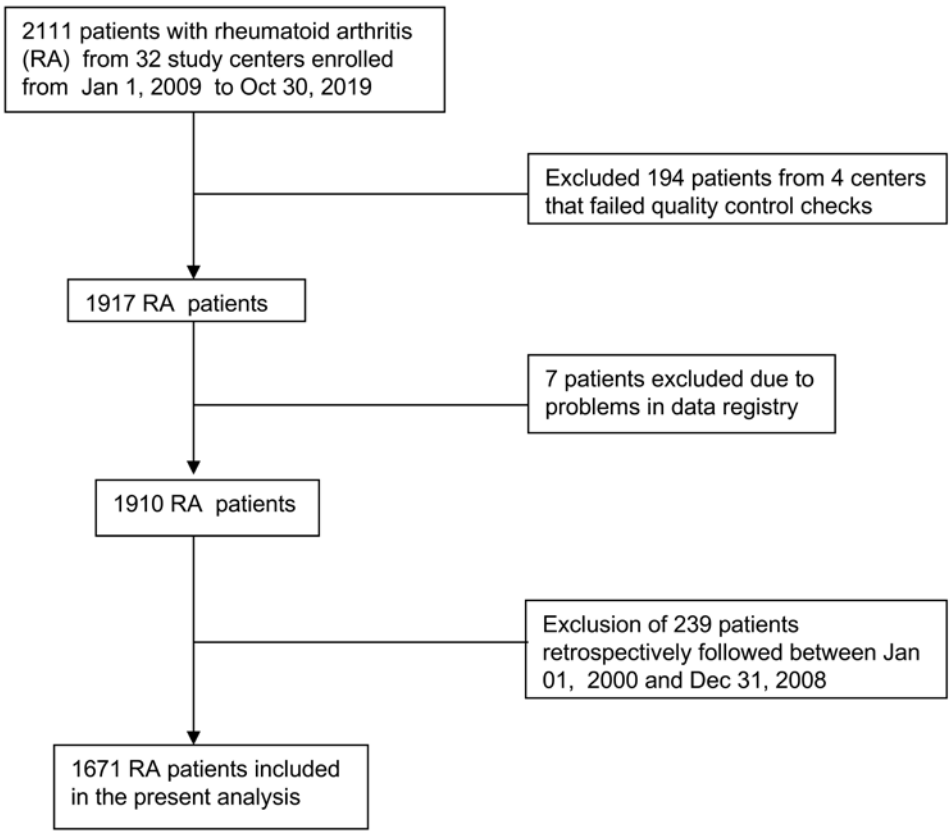

Figure 1. Flowchart describing the enrollment of patients.

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Table 1. Baseline clinical and demographic features of the patients followed up in the cohort. The medications represent those used concurrently during the first treatment course.

	Neither MTX nor LEF, n = 156	MTX, n = 766	LEF, n = 297	MTX + LEF, n = 452	*P**
Female	125 (80.1)	651 (85.0)	261 (87.9)	393 (86.9)	0.12
Age, yrs, mean (SD)	54.7 (14.2)	50.7 (12.0)	52.2 (11.8)	50.7 (11.6)	0.001
Disease duration, yrs, median (IQR)	7.7 (2.6–17.0)	4.6 (1.0–11.1)	7.0 (3.1–13.6)	5.7 (1.9–12.3)	< 0.001
Seropositive RA (RF or anti-CCP)	136 (87.2)	679 (88.6)	251 (84.5)	367 (81.2)	0.004
DAS28 at baseline[a], mean (SD)	5.15 (1.49)	5.24 (1.57)	5.20 (1.41)	5.08 (1.36)	0.33
Current smoking	15 (9.6)	115 (15.0)	38 (12.8)	79 (17.5)	0.08
History of malignancy	4 (2.6)	8 (1.0)	4 (1.3)	6 (1.3)	0.47
Diabetes	24 (15.4)	86 (11.2)	47 (15.8)	58 (12.8)	0.17
Hypertension	61 (39.1)	271 (35.4)	131 (44.1)	176 (38.9)	0.07
Hypercholesterolemia	27 (17.3)	82 (10.7)	50 (16.8)	71 (15.7)	0.01
Osteoporosis	34 (21.8)	88 (11.5)	46 (15.5)	74 (16.4)	0.003
Hepatitis C	5 (3.2)	1 (0.1)	0 (0.0)	1 (0.2)	< 0.001
Hepatitis B	1 (0.6)	6 (0.8)	2 (0.7)	2 (0.4)	0.94
Kidney failure	7 (4.5)	5 (0.7)	3 (1.0)	1 (0.2)	0.001
Ischemic cardiomyopathy	4 (2.6)	13 (1.7)	5 (1.7)	5 (1.1)	0.58
COPD	2 (1.3)	14 (1.8)	9 (3.0)	12 (2.7)	0.5
Heart failure	2 (1.3)	4 (0.5)	2 (0.7)	4 (0.9)	0.58
Corticosteroid	117 (75.0)	602 (78.6)	232 (78.1)	380 (84.1)	0.04
HCQ or CQ	37 (23.7)	201 (26.2)	38 (12.8)	107 (23.7)	< 0.001
Sulfasalazine	18 (11.5)	31 (4.0)	9 (3.0)	12 (2.7)	< 0.001
Anti-TNF agents	99 (63.5)	457 (59.7)	212 (71.4)	243 (53.8)	< 0.001
Other biologics[b]	27 (17.3)	51 (6.7)	18 (6.1)	11 (2.4)	< 0.001
JAK inhibitor (tofacitinib)	19 (12.2)	27 (3.5)	10 (3.4)	3 (0.7)	< 0.001
Starting yr, mean (SD)	2013.7 (3.0)	2012.4 (3.1)	2013.1 (3.1)	2012.1 (2.7)	< 0.001

Data are presented as n (%), except when indicated otherwise. [a] Data on DAS28 for 7 patients were not available. [b] Other biologics are abatacept, rituximab, or tocilizumab. * Pearson chi-square, Fisher exact test, ANOVA, or Kruskal-Wallis test, according to the nature and distribution of data. Anti-CCP: anticyclic citrullinated peptide; COPD: chronic obstructive pulmonary disease; CQ: chloroquine; DAS28: Disease Activity Score in 28 joints; HCQ: hydroxychloroquine; JAK: Janus kinase; LEF: leflunomide; MTX: methotrexate; RA: rheumatoid arthritis; RF: rheumatoid factor; TNF: tumor necrosis factor.

Table 2. Results of Cox proportional hazards models testing the association of MTX + LEF with AEs in comparison to a group representing use of MTX or LEF.

	Type of AE (n)	MTX + LEF, n = 452 Rate Per 100 PY (95% CI)	MTX or LEF, n = 1063 Rate per 100 PY (95% CI)	HR (95% CI), *P* Crude Analysis[a]	HR (95% CI), *P* Adjusted for Covariates[a,b]
Total serious AEs (298)		5.4 (4.4–6.6)	5.4 (4.7–6.2)	1.01 (0.78–1.31), 0.92	1.00 (0.76–1.31), 0.98
Fatal AEs (26)		0.5 (0.2–0.9)	0.4 (0.2–0.6)	1.27 (0.53–3.02), 0.59	1.23 (0.46–3.30), 0.68
Any AE (854)		26.5 (23.8–29.4)	22.2 (20.6–24.0)	1.16 (1.00–1.34), 0.06	1.22 (1.04–1.42), 0.01
Cardiovascular[c]	Serious (40)	0.8 (0.4–1.3)	0.6 (0.4–0.9)	1.30 (0.66–2.58), 0.45	1.04 (0.49–2.21), 0.92
	Total (106)	2.5 (1.9–3.4)	1.6 (1.3–2.1)	1.56 (1.04–2.32), 0.03	1.33 (0.87–2.03), 0.18
Infections	Serious (144)	2.6 (1.9–3.5)	2.3 (1.9–2.9)	1.16 (0.80–1.67), 0.44	1.24 (0.84–1.82), 0.28
	Total (458)	10.8 (9.2–12.6)	9.5 (8.5–10.6)	1.14 (0.93–1.40), 0.21	1.26 (1.02–1.56), 0.03
Hepatic[c]	Serious (8)	0.2 (0.06–0.5)	0.1 (0.05–0.3)	ND	ND
	Total (42)	0.9 (0.5–1.5)	0.6 (0.4–0.9)	1.48 (0.77–2.83), 0.24	1.44 (0.72–2.85), 0.30
Hematologic	Serious (12)	0.2 (0.1–0.6)	0.2 (0.1–0.4)	1.51 (0.43–5.35), 0.52	ND
	Total (49)	1.0 (0.6–1.6)	0.8 (0.5–1.1)	1.28 (0.69–2.36), 0.44	1.17 (0.62–2.21), 0.63
Respiratory tract[c]	Serious (16)	0.2 (0.1–0.6)	0.3 (0.1–0.5)	0.87 (0.27–2.78), 0.82	ND
	Total (57)	0.8 (0.5–1.4)	1.1 (0.8–1.5)	0.91 (0.49–1.70), 0.77	1.05 (0.55–2.00), 0.88
Gastrointestinal[c]	Serious (15)	0.2 (0.1–0.6)	0.3 (0.1–0.5)	0.89 (0.28–2.84), 0.84	ND
	Total (102)	1.9 (1.3–2.6)	1.7 (1.3–2.2)	1.09 (0.71–1.68), 0.69	1.06 (0.68–1.67), 0.78

[a] These analyses include 1671 patients, since 156 patients taking neither MTX nor LEF are accounted for in multivariate analysis. [b] Adjusted for age, baseline DAS28, disease duration, sex, current smoking, seropositivity for rheumatoid factor or anti-CCP, history of malignancy, diabetes, hypertension, hypercholesterolemia, renal failure, ischemic cardiomyopathy, COPD, heart failure, use of sulfasalazine, antimalarials, biologic DMARDs/tofacitinib, corticosteroids, starting year, osteoporosis, and hepatitis B and C. [c] Excluding infections of any kind. AE: adverse event; anti-CCP: anticyclic citrullinated peptide; COPD: chronic obstructive pulmonary disease DAS28: Disease Activity Score in 28 joints; DMARD: disease-modifying antirheumatic drug; LEF: leflunomide; MTX: methotrexate; ND: not done due to small number of events (< 10 for crude analysis and < 20 for multivariate analysis); PY: patient-years.

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multivariate models presented in Table 2, antimalarials were significantly protective for SAEs (adjusted HR [aHR] 0.73, 95% CI 0.55–0.98, $P = 0.04$) and total hepatic AEs (aHR 0.26, 95% CI 0.09–0.74, $P = 0.012$). SSZ was related to higher hazards of SAEs (aHR 2.35, 95% CI 1.49–3.71, $P < 0.001$), total AEs (aHR 1.60, 95% CI 1.16–2.20, $P = 0.004$), total hematologic events (aHR 3.36, 95% CI 1.16–9.75, $P = 0.03$), and total (aHR 1.81, 95% CI 1.18–2.76, $P = 0.006$) and serious infections (aHR 2.08, 95% CI 1.06–4.06, $P = 0.033$). bDMARDs/JAKis were associated with higher hazards of SAEs (aHR 1.49, 95% CI 1.12–1.98, $P = 0.006$), total AEs (aHR 1.61, 95% CI 1.36–1.90, $P < 0.001$), and total (aHR 2.10, 95% CI 1.65–2.67, $P < 0.001$) and serious infections (aHR 2.53, 95% CI 1.61–3.96, $P < 0.001$).

In an alternative analysis, we compared the hazard of SAE of MTX + LEF with a category representing the use of MTX, adjusting for potential confounding variables (Supplementary Table 3, available with the online version of this article). Again, there was no significant increase in risk of SAE (aHR 1.02, 95% CI 0.77–1.36, $P = 0.89$) with MTX + LEF.

Considering the risk of laboratory abnormalities comparing MTX + LEF with the MTX or LEF group, there were numerically higher incidence of anemia (aHR 0.7, 95% CI 0.4–1.2 per 100 PY vs aHR 0.4, 95% CI 0.2–0.6 per 100 PY, respectively), and elevation of hepatic transaminases (aHR 0.6, 95% CI 0.3–1.1 per 100 PY vs aHR 0.3, 95% CI 0.1–0.5 per 100 PY, respectively) in the former group. Univariate HRs for the comparisons listed above were 1.91 (95% CI 0.88–4.13, $P = 0.10$) and 2.28 (95% CI 0.95–5.48, $P = 0.07$), respectively. The incidence of neutropenia was 0.1 (95% CI < 0.1–0.5) per 100 PY in the MTX + LEF group compared to 0.2 (95% CI 0.1–0.4) per 100 PY in the MTX or LEF group (HR 0.74, 95% CI 0.15–3.66, $P = 0.71$). However, these analyses may be limited by the small number of events recorded (anemia, elevation of hepatic transaminases, and neutropenia represented only 30, 22, and 10 events, respectively).

MTX + LEF vs bDMARDs/JAKi (with MTX or LEF). Table 3 shows the comparison of the hazards of primary and secondary outcomes between MTX + LEF and the combination of bDMARDs or JAKi with MTX or LEF (reference category). The patients' features are described in Supplementary Table 4 (available with the online version of this article). There was a significant reduction in the hazards of SAEs, and total and serious infections with MTX + LEF compared to the reference group. Figure 2 shows the comparison of the cumulative incidence of SAEs between the groups. Exclusively comparing patients receiving MTX + LEF with those on MTX + bDMARDs/tofacitinib, similar results were observed (Supplementary Table 5).

MTX + LEF vs MTX + SSZ. Supplementary Table 6 (available with the online version of this article) describes the patients' features and Supplementary Table 7 compares the hazards of SAEs and secondary outcomes of MTX + LEF and MTX + SSZ. A reduction in the hazards of SAEs (aHR 0.33, 95% CI 0.16–0.65, $P = 0.002$) and total hematologic events (HR 0.26, 95% CI

Table 3. Results of Cox proportional hazards models comparing the hazard of AEs of MTX + LEF vs biologic agents/JAK inhibitor (combined with either MTX or LEF).

		MTX + LEF, n = 195	Biologic Agents/JAK Inhibitor (With MTX or LEF), n = 775	HR (95% CI), *P*	
	Type of AE (n)	Rate per 100 PY (95% CI)	Rate per 100 PY (95% CI)	Crude Analysis[a]	Adjusted for Covariates[a,b]
Total serious AEs (156)		3.0 (2.1–4.5)	5.5 (4.7–6.5)	0.61 (0.40–0.94), 0.02	0.56 (0.36–0.88), 0.01
Fatal AEs (11)		0.3 (0.1–1.0)	0.3 (0.2–0.6)	1.1 (0.29–4.18), 0.89	ND
Any AE (509)		19.7 (16.6–23.5)	25.7 (23.7–28.0)	0.83 (0.66–1.03), 0.09	0.80 (0.64–1.00), 0.06
Cardiovascular[c]	Serious (16)	0.6 (0.2–1.4)	0.4 (0.2–0.8)	1.42 (0.49–4.11), 0.52	ND
	Total (52)	1.8 (1.1–2.9)	1.5 (1.1–2.0)	1.26 (0.69–2.30), 0.45	0.85 (0.44–1.64), 0.62
Infections	Serious (78)	1.2 (0.7–2.3)	2.7 (2.1–3.4)	0.53 (0.28–1.00), 0.05	0.48 (0.25–0.94), 0.03
	Total (282)	7.2 (5.5–9.4)	11.7 (10.4–13.2)	0.70 (0.51–0.94), 0.02	0.70 (0.51–0.96), 0.03
Hepatic[c]	Serious (2)	0.0 (NA)	0.1 (< 0.1–0.3)	ND	ND
	Total (23)	0.9 (0.5–1.9)	0.6 (0.4–1.0)	1.72 (0.73–4.07), 0.22	2.03 (0.80–5.12), 0.14
Hematologic	Serious (4)	0.2 (0.1–0.9)	0.1 (< 0.1–0.3)	ND	ND
	Total (29)	1.1 (0.6–2.0)	0.8 (0.5–1.2)	1.40 (0.64–3.09), 0.40	1.76 (0.75–4.11), 0.19
Respiratory tract[c]	Serious (9)	0.2 (0.1–0.9)	0.3 (0.1–0.6)	ND	ND
	Total (31)	0.7 (0.3–1.5)	1.0 (0.7–1.4)	0.74 (0.30–1.81), 0.508	0.91 (0.34–2.41), 0.85
Gastrointestinal[c]	Serious (7)	0.1 (< 0.1–0.8)	0.2 (0.1–0.5)	ND	ND
	Total (59)	1.8 (1.1–2.9)	1.7 (1.3–2.3)	1.02 (0.56–1.84), 0.954	1.19 (0.63–2.25), 0.59

[a] These analyses include 970 patients. [b] Adjusted for age, baseline DAS28, disease duration, sex, current smoking, seropositivity for rheumatoid factor or anti-CCP, history of malignancy, diabetes, hypertension, hypercholesterolemia, renal failure, ischemic cardiomyopathy, COPD, heart failure, use of sulfasalazine, antimalarials, biologic DMARDs/tofacitinib, corticosteroids, starting year, osteoporosis, and hepatitis B and C. [c] Excluding infections of any kind. AE: adverse event; anti-CCP: anticyclic citrullinated peptide; COPD: chronic obstructive pulmonary disease; DAS28: Disease Activity Score in 28 joints; DMARD: disease-modifying antirheumatic drug; JAK: Janus kinase; LEF: leflunomide; MTX: methotrexate; NA: not applicable; ND: not done due to small number of events (< 10 for crude analysis and < 20 for multivariate analysis); PY: patient-years.

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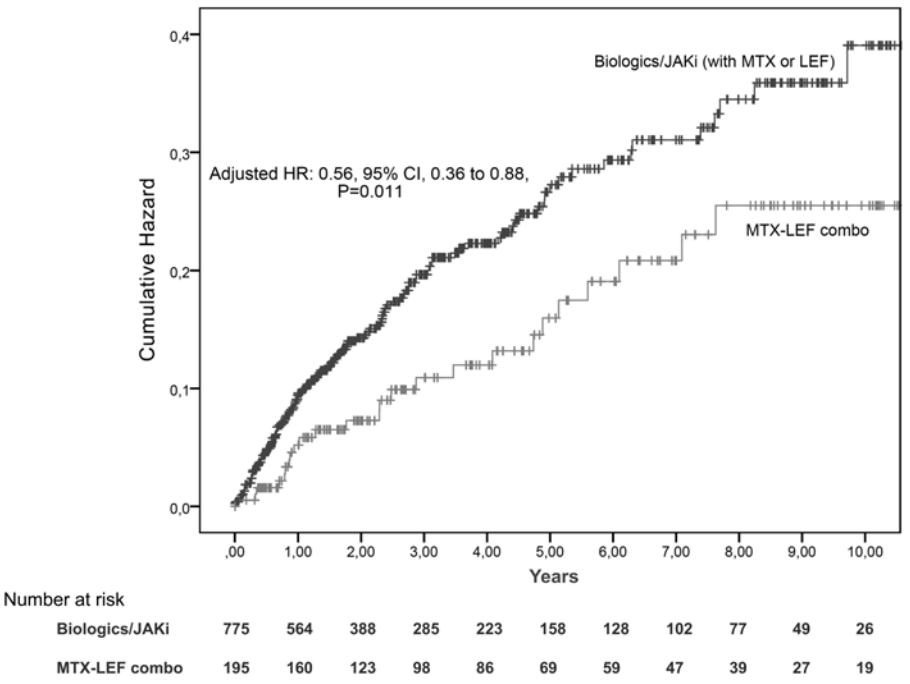

Figure 2. Kaplan-Meier curves comparing the cumulative incidence of serious adverse events between patients taking MTX + LEF and those taking bDMARDs/JAKis with MTX or LEF. The vertical traces represent censored patients. bDMARD: biologic disease-modifying antirheumatic drug; JAKi: Janus kinase inhibitor; LEF: leflunomide; MTX: methotrexate.

0.08–0.90, $P = 0.03$) was observed with the use of MTX + LEF.

Analysis of drug survival. The comparison of hazard of interruption of treatment is shown in Supplementary Table 8 (available with the online version of this article). MTX + LEF was associated with lower hazards of interruption as a result of AEs or death (aHR 0.31, 95% CI 0.17–0.58, $P < 0.001$) and for any reason (aHR 0.76, 95% CI 0.61–0.95, $P = 0.02$; Figure 3) in comparison to bDMARDs/JAKi (with MTX or LEF). There was no difference in the hazard of interruption because of inefficacy (aHR 0.84, 95% CI 0.62–1.12, $P = 0.24$). MTX + LEF was related to lower hazards of therapy interruption for any reason (HR 0.62, 95% CI 0.39–0.98, $P = 0.04$) and because of AEs (aHR 0.38, 95% CI 0.15–0.96, $P = 0.04$) in comparison to MTX + SSZ.

MTX + LEF vs MTX/LEF among patients treated with bDMARDs or JAKi. Considering the relatively large number (n = 257) of patients on MTX + LEF along with bDMARDs/JAKi (MLB/J group), we compared these patients with those also using bDMARDs/JAKi, but with MTX or LEF (reference category). Patients' features are described in Supplementary Table 9 (available with the online version of this article). SAEs (HR 1.41, 95% CI 1.03–1.92, $P = 0.03$), total AEs (aHR 1.21, 95% CI 1.00–1.46, $P = 0.05$), and total CV events (aHR 2.04, 95% CI 1.21–3.41, $P = 0.007$) presented higher incidence in the MLB/J group, whereas serious infections (HR 1.50, 95% CI 0.99–2.29, $P = 0.06$) tended to occur more frequently in the MLB/J group than in the reference category (Supplementary Table 10, available with the online version of this article).

Sensitivity analyses. We performed different sensitivity analyses, removing possible preset combinations of MTX + LEF eventually transposed to the current treatment course, controlling the analysis for treatment center and for individual bDMARD/JAKi used (Supplementary Text 3 and Supplementary Tables 11–13, available with the online version of this article), confirming the results previously presented. A comparison of hazard of SAE between MTX + LEF and each individual bDMARD/JAKi (with and without MTX or LEF) is shown in Supplementary Table 14. The tests of the proportional hazard assumption are described in Supplementary Text 3 and in Supplementary Figure 1.

The results obtained with traditional multivariate Cox methods were reevaluated using PSMA (see Supplementary Data 1, available with the online version of this article), and the results of both types of analyses were very similar.

DISCUSSION

In the present study, the combination of MTX and LEF presented a safety profile comparable to that of the uncombined use of both drugs. Despite the increased frequency of total AEs (mainly infections and CV events), the incidence of serious infections, serious CV events, and total SAEs was not significantly changed with the combination. Comparing MTX + LEF with biologic agents/JAKi (plus MTX or LEF), there were reductions of 50–60% in the hazard of SAEs and serious infections. The incidence of treatment interruption (especially because of AEs) was also lower with MTX + LEF, suggesting that this combination has an acceptable safety profile in patients

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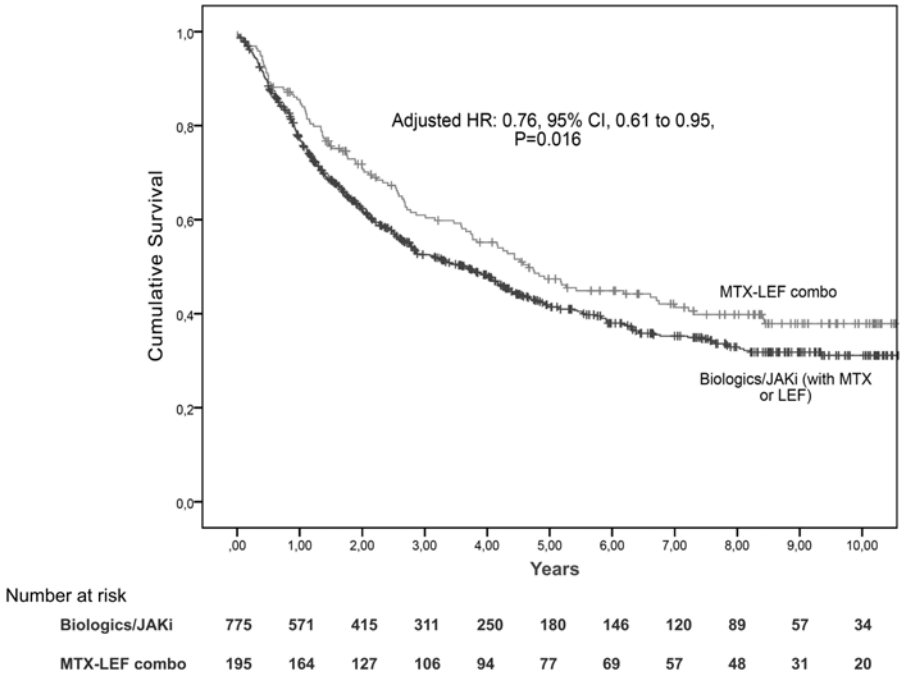

Figure 3. Kaplan-Meier curves comparing the survival of treatment course between patients taking MTX + LEF and those using bDMARDs/JAKis (with MTX or LEF). The vertical traces represent censored patients. bDMARD: biologic disease-modifying antirheumatic drug; JAKi: Janus kinase inhibitor; LEF: leflunomide; MTX: methotrexate.

with RA who fail treatment with monotherapy or other combinations of csDMARDs. However, among patients using bDMARDs, concomitant use of MTX and LEF was associated with higher hazard of SAEs in univariate analysis.

The efficacy of the MTX-LEF combination in RA has been demonstrated in 2 RCTs, showing superiority compared to MTX alone[9] and suggesting equivalence with MTX plus low-dose RTX[10] in patients failing therapy with MTX. However, results from the CareRA trial failed to demonstrate better efficacy of the MTX-LEF-prednisone combination in comparison to MTX plus prednisone in DMARD-naïve patients with RA.[38] In these 3 RCTs, there was no increase in the risk of SAEs with MTX + LEF.[9,10,38] The safety profile of MTX + LEF has also been evaluated in observational[11,12,14–23,25–27,39] and noncontrolled experimental studies,[24,29,40,41,42,43] but most of these studies followed up patients for < 1 year. The largest study to date is the retrospective cohort based on a healthcare-system database by Cannon, *et al*,[14] including 2048 patients (1415 PYs) on MTX + LEF. This study found even a lower incidence of reported AEs with MTX + LEF in relation to other combinations involving these drugs. On the other hand, Curtis, *et al*[11] observed a 4-fold increase in the hazard of elevation of transaminases ≥ the 2-fold upper limit of normal with MTX (≥ 7.5 mg/d) + LEF (20 mg/d). These results were similar to those observed in the RCT by Kremer, *et al*.[9] Lee, *et al*,[12] in a prospective cross-sectional study, observed a higher prevalence ratio of liver-silent fibrosis measured by elastography in patients with MTX + LEF, and correlated it with the cumulative dose of LEF. In our study, the incidence of serious and nonserious hepatic AEs (including elevation of liver enzymes) was only numerically higher with MTX + LEF, but the number of events was smaller than expected and conclusions on hepatic safety cannot be drawn from our data.

Hematologic AEs (mainly neutropenia and pancytopenia) are other feared complications related to the combination of MTX and LEF. Pancytopenia has been reported to occur in 1 of 4000 patients under LEF treatment and in 1 of 575–822 patients with the MTX-LEF combination.[13] In the present study, we observed a numerically higher hazard of hematologic events with the use of MTX + LEF, but these events represented a relatively small fraction of all SAEs.

In the multivariate survival models presented in this study, the use of SSZ was associated with increased hazard of SAEs, hematologic AE, and serious infections, whereas antimalarials protected for SAEs and reduced the incidence of hepatic events. MTX + SSZ was associated with higher hazard of AE-related interruption of treatment as well as higher hazard of SAEs in comparison to the MTX-LEF association. These analyses were limited by the small number of patients using SSZ (n = 70), but our results agree with previous evidence suggesting low tolerability of SSZ in RA in settings outside clinical trials.[6,7,8]

Our study has several strengths. To the best of our knowledge, this is the largest cohort study (in terms of number of PYs) of individuals on treatment with MTX + LEF, and the first to compare its safety with schemes involving bDMARDs. Quality of data was regularly checked in this multicentric registry-based study. We performed several sensitivity analyses to reduce the risk of selection bias (including "immortal time

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bias" by comparing only new-onset MTX-LEF combinations with novel combinations of bDMARDs/JAKi + csDMARDs) and confounding bias. The results obtained with traditional multivariate survival analyses were reconfirmed using PSMA.

The present study also has limitations. Inclusion of patients in the cohort and the choice of therapeutic regimens were decisions of the investigators of each center, creating room for selection and channeling bias. A retrospective follow-up period was permitted up to 6 months after the start of a treatment course. This may possibly act in favor of selection of schemes that survived the initial months of therapy. However, a relatively large number of SAEs (26.2%) were recorded within the first 6 months of follow-up, and excluding patients with < 6 months of follow-up (whose SAEs could have been retrospectively recorded) did not change the results significantly (see Supplementary Text 3, available with the online version of this article).

Further limitations of this study include the fact that, despite the use of multivariate analysis, unaccounted residual confounding may still affect hazard estimates. Our data bank has no record of dosing and route of administration of DMARDs, which, especially in the case of the combination of MTX and LEF, are factors that may affect the incidence of AEs. Some analyses presented in this article were limited by the reduced number of patients taking SSZ. The number of patients on non–antitumor necrosis factor bDMARDs and JAKis is also small, reducing the reliability of specific analyses with these subgroups of drugs. The centers participating in this study were all located in Brazil, a multiethnic South American developing country; this may have an effect on the external validity of the results. We observed a lower-than-expected number of patients with elevation of hepatic transaminases, indicating that subclinical hepatic events were probably underreported in this study. There was no fixed schedule or predefined thresholds above or below which laboratory abnormalities should have been reported, and minor hematologic AEs may also have been subnotified.

Our results suggest that the combination of MTX + LEF may present a relatively good safety and tolerability profile in comparison to MTX + SSZ and schemes involving advanced therapies in RA. Further studies performed in different clinical and sociodemographic settings are necessary to confirm these findings.

ACKNOWLEDGMENT

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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Correction

Safety of the Methotrexate–leflunomide Combination in Rheumatoid Arthritis: Results of a Multicentric, Registry-based, Cohort Study (BiobadaBrasil)

Markus Bredemeier, Roberto Ranza, Adriana M. Kakehasi, Aline Ranzolin, Inês G. da Silveira, Ana C.M. Ribeiro, David C. Titton, André L.S. Hayata, Hellen M.S. Carvalho, Bárbara S. Kahlow, Vander Fernandes, Paulo Louzada Jr., Manoel B. Bértolo, Ângela L.B.P. Duarte, José C. Macieira, José R.S. Miranda, Geraldo R.C. Pinheiro, Reginaldo B. Teodoro, Marcelo M. Pinheiro, Valéria Valim, Ivânio A. Pereira, Maria F.L.C. Sauma, Gláucio R.W. de Castro, Laurindo F. da Rocha Jr., Sâmia A.S. Studart, Morgana O. Gazzeta, Leticia G. da Silveira, Cristiano M. Lupo, and Ieda M.M. Laurindo

J Rheumatol 2021; doi: 10.3899/jrheum.201248

In the Results section, under the subheading, "Comparison of MTX + LEF with MTX/LEF," the first sentence in the third paragraph should not include adjusted HRs (aHRs) as the values refer to crude incidence: "Considering the risk of laboratory abnormalities comparing MTX + LEF with the MTX or LEF group, there were numerically higher incidence of anemia (0.7, 95% CI 0.4–1.2 per 100 PY vs 0.4, 95% CI 0.2–0.6 per 100 PY, respectively), and elevation of hepatic transaminases (0.6, 95% CI 0.3–1.1 per 100 PY vs 0.3, 95% CI 0.1–0.5 per 100 PY, respectively) in the former group." In the Table 3 footnotes, biologic DMARDs/tofacitinib should not be included in the legend "b". The correct legend is, "[b] Adjusted for age, baseline DAS28, disease duration, sex, current smoking, seropositivity for rheumatoid factor or anti-CCP, history of malignancy, diabetes, hypertension, hypercholesterolemia, renal failure, ischemic cardiomyopathy, COPD, heart failure, use of sulfasalazine, antimalarials, corticosteroids, starting year, osteoporosis, and hepatitis B and C." The errors do not affect the results or conclusions of the study.

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