SAFETY OF THE METHOTREXATE-LEFLUNOMIDE COMBINATION IN RHEUMATOID ARTHRITIS: RESULTS OF A MULTICENTRIC, REGISTRY-BASED, COHORT STUDY (BIOBADABRASIL)

Markus Bredemeier [0000-0002-7911-593X], Roberto Ranza [0000-0002-6855-2413], Adriana Maria Kakehasi [0000-0001-9411-7493], Aline Ranzolin [0000-0002-8260-2288], Inês Guimarães da Silveira, Ana Cristina de Medeiros Ribeiro [0000-0001-7168-5906], David Cezar Titton, André Luiz Shinji Hayata, Hellen Mary Silveira Carvalho, Bárbara Stadler Kahlow, Vander Fernandes, Paulo Louzada Jr., Manoel Barros Bértolo, Ângela Luzia Branco Pinto Duarte, José Caetano Macieira, José Roberto Silva Miranda, Geraldo da Rocha Castelar Pinheiro, Reginaldo Botelho Teodoro, Marcelo de Medeiros Pinheiro, Valéria Valim, Ivânio Alves Pereira, Maria de Fátima Lobato da Cunha Sauma, Gláucio Ricardo Werner de Castro, Laurindo Ferreira da Rocha Jr., Sâmia Araujo de Sousa Studart, Morgana Ohira Gazzeta, Leticia Guimarães da Silveira, Cristiano Michelini Lupo, Ieda Maria Magalhães Laurindo.

Key indexing terms: arthritis, rheumatoid; antirheumatic drugs, disease modifying; drug safety; methotrexate; leflunomide; biologics.

From Hospital Nossa Senhora da Conceição, Grupo Hospitalar Conceição, Porto Alegre; Universidade Federal de Uberlândia, Uberlândia; Hospital das Clínicas da Universidade Federal de Minas Gerais, Belo Horizonte; Universidade Federal de Pernambuco (UFPE), Recife; Hospital São Lucas, Faculdade de Medicina da PUCRS, Porto Alegre; Hospital das Clínicas da Faculdade de Medicina da USP (HCFMUSP), São Paulo; Universidade Federal do Paraná, Curitiba; Clínica de Reumatologia, Osasco; Hospital de Base do Distrito Federal, Brasília;

Hospital Universitário Evangélico de Curitiba, Curitiba; Hospital Geral Universitário de Cuiabá, Cuiabá; Faculdade de Medicina USP, Ribeirão Preto; Universidade Estadual de Campinas, Campinas; Universidade Federal de Sergipe, Aracajú; Artrocenter Clínica Médica de Taubaté, Taubaté; Universidade Estadual do Rio de Janeiro, Rio de Janeiro; Hospital da Universidade Federal do Triângulo Mineiro, Uberaba; Universidade Federal de São Paulo, São Paulo; Universidade Federal do Espírito Santo, Vitória; Hospital Universitário da Universidade Federal de Santa Catarina, Florianópolis; Universidade Federal do Pará, Belém; Hospital Governador Celso Ramos, Florianópolis; Instituto de Medicina Integral Prof. Fernando Figueira (IMIP), Recife; Hospital Geral de Fortaleza, Fortaleza; Santa Casa de Misericórdia do Rio de Janeiro, Rio de Janeiro; Universidade Federal do Rio Grande do Sul/Hospital de Clínicas de Porto Alegre, Porto Alegre; Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto; Faculdade de Medicina da Universidade Nove de Julho, São Paulo, Brazil.

Conflicts of interest. The authors declare having no conflict of interest related to the content of this paper.

M. Bredemeier, MD, PhD, Hospital Nossa Senhora da Conceição, Grupo Hospitalar Conceição; R. Ranza, MD, PhD, Universidade Federal de Uberlândia; A.M. Kakehasi, MD, PhD, Hospital das Clínicas da Universidade Federal de Minas Gerais; A. Ranzolin, MD, PhD, Universidade

Federal de Pernambuco (UFPE); I.G. da Silveira, MD, PhD, Hospital São Lucas, Faculdade de Medicina da PUCRS; A.C. Ribeiro, MD, PhD, Hospital das Clínicas da Faculdade de Medicina da USP (HCFMUSP); D.C. Titton, MD, Universidade Federal do Paraná; A.L. Hayata, MD, PhD, Clínica de Reumatologia (Osasco); H.M. Carvalho, MD, Hospital de Base do Distrito Federal; B.S. Kahlow, MD, MSc, Hospital Universitário Evangélico de Curitiba; V. Fernandes, MD, PhD, Hospital Geral Universitário de Cuiabá; P. Louzada Jr., MD, PhD, Faculdade de Medicina USP; M. Bértolo, MD, PhD, Universidade Estadual de Campinas; A.L. Duarte, MD, PhD, Universidade Federal de Pernambuco (UFPE); J.C. Macieira, MD, MSc, Universidade Federal de Sergipe; J.R. Miranda, MD, Artrocenter Clínica Médica de Taubaté; G.R. Pinheiro, MD, PhD, Universidade Estadual do Rio de Janeiro; R.B. Teodoro, MD, MSc, Hospital da Universidade Federal do Triângulo Mineiro; M.M. Pinheiro, MD, PhD, Universidade Federal de São Paulo; V. Valim, MD, PhD, Universidade Federal do Espírito Santo; I.A. Pereira, MD, PhD, Hospital Universitário da Universidade Federal de Santa Catarina; M.F. Sauma, MD, PhD, Universidade Federal do Pará; G.R. de Castro, MD, Hospital Governador Celso Ramos; L.F. da Rocha Jr., MD, PhD, Instituto de Medicina Integral Prof. Fernando Figueira (IMIP); S.A. Studart, MD, MSc, Hospital Geral de Fortaleza; M.O. Gazzeta, MD, Santa Casa de Misericórdia do Rio de Janeiro; L.G. da Silveira, MS, Universidade Federal do Rio Grande do Sul/Hospital de Clínicas de Porto Alegre; C.M. Lupo, MD, Faculdade de Medicina de São José do Rio Preto; I.M. Laurindo, MD, PhD, Faculdade de Medicina da Universidade Nove de Julho.

Address correspondence to:

Dr. Markus Bredemeier, Serviço de Reumatologia do Hospital Nossa Senhora da Conceição, Avenida Francisco Trein, 596, Bloco H, 3º andar, Porto Alegre, RS, 91350-200, Brazil. E-mail: markbred@terra.com.br. Phone: +55-51-33572493.

Running title: Safety of MTX+LEF.

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 anti-rheumatic drugs (DMARDs) or JAK inhibitors (JAKi).

Methods. RA patients starting the first treatment course with a csDMARD (without previous use of biologic or JAKi) or 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 matched analysis (PSMA) were used for statistical comparisons.

Results. In total, 1671 patients (5349 patient-years [PY]) were enrolled; 452 patients (1537 PY) received MTX plus LEF. The overall incidence of SAEs was 5.6/100 PY. The hazard of SAEs for MTX plus LEF was not higher than for MTX or LEF (adjusted hazard ratio: 1.00, 95% CI, 0.76 to 1.31, P=0.984). The MTX-LEF combo presented a lower hazard of SAEs (0.56, 0.36 to 0.88, P=0.011) and infectious SAEs (0.48, 0.25 to 0.94, P=0.031) than bDMARDs/JAKi with MTX or LEF. MTX plus LEF presented lower hazard of SAEs than MTX plus SSZ (0.33, 0.16 to 0.65, P=0.002). Analysis using PSMA confirmed the results obtained with traditional multivariate Cox analysis.

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

INTRODUCTION

The use of conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs), especially methotrexate, is the first step in the treatment of rheumatoid arthritis (RA). After failure of methotrexate (MTX) monotherapy, it is possible to step-up treatment using combinations of csDMARDs (1-3), 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 bDMARDs in randomized controlled trials (4,5). However, recent evidence has questioned the effectiveness of triple therapy in RA (6-8), mainly because of the relatively poor tolerability of sulfasalazine (6,7). A possible alternative to triple therapy is the association of MTX and leflunomide (MTX-LEF combo), which has shown higher efficacy than monotherapy with MTX (9) and similar efficacy comparing with MTX plus rituximab (10). However, the MTX-LEF combo 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 with MTX plus LEF in comparison to other schemes of csDMARDs. Other studies on MTX plus 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 JAKi. Considering that, in the present study our aim is to assess the safety of the MTX-LEF combo in a registry-based cohort of RA patients, comparing it with other therapeutic schemes including csDMARDs and advanced therapies for RA.

MATERIALS AND 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 biologic therapies (and more recently, JAKi), but patients starting treatment with a csDMARDs 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 had 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 a written informed consent (29). The study was performed in compliance with the principles of the Declaration of Helsinki.

Patients

For the present study, we selected exclusively patients with RA according to 1987 ACR criteria (31) or the 2010 EULAR/ACR criteria (32), starting a new csDMARD (sulfasalazine, antimalarials, cyclosporin, methotrexate or leflunomide, with no previous exposure to bDMARDs) or the 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 was overlapping with other connective tissues diseases, except for secondary Sjögrens's syndrome. Recruitment of patients to BiobadaBrasil started on 1st Jan 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 record of clinical and demographic features, therapeutic scheme and adverse events 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 the MTX-LEF combo in the treatment of RA in comparison to other schemes. Initially, we compared the hazard of adverse events of MTX plus LEF and a control group using either MTX or LEF (not in combination with each other). Next, we compared patients using the MTX-LEF combo with those receiving biologic agents or JAKi along with MTX or LEF. Analysis was also performed comparing the MTX-LEF combo with MTX and with MTX plus biologics/JAKi. As a secondary goal, we compared the hazards of adverse events of MTX plus LEF with those of the combination of methotrexate and sulfasalazine (MTX-SSZ combo). In an exploratory analysis, we compared patients receiving bDMARDs/JAKi (with MTX or LEF) with those receiving bDMARDs/JAKi with MTX plus LEF. Confounding variables (recorded at baseline) considered here were Disease Activity Score in 28 joints (DAS28), gender, age, seropositivity (forrheumatoid fator and/or anti-cyclic citrullinated peptide), duration of disease, smoking, diabetes, hypertension, renal failure, ischemic cardiomyopathy, heart failure, history of cancer, chronic obstructive pulmonary disease (COPD), concurrent use of biologics/JAK inhibitor, sulfasalazine, antimalarials (hydroxychloroquine or chloroquine), and corticosteroids, starting year, hypercholesterolemia, osteoporosis, and hepatitis B and C. Study center was also included as independent variable in some sensitivity analyses and in all propensity score matched analyses.

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 adverse event, a local investigator filled a common web-based platform, actively looking for a list of adverse events based on MedDRA (Medical Dictionary for Drug Regulatory Activities) nomenclature (34). Data collection and record in databank occurred whenever adverse events were detected during regular or unscheduled visits or a change in treatment regimen was done. Relevant adverse events were collected both spontaneously and by active physician interrogation about common side effects, as well 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 adverse event was mandatory. Definitions of severity and outcomes of adverse events were stated in the BiobadaBrasil protocol (29). A serious adverse event (SAE) required immediate notification and was defined as a condition that causes death or is life threatening, leads to inpatient hospitalization or prolongation of an existing one, causes 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 (including stroke), hepatic, hematologic, respiratory tract, and gastrointestinal AEs. The Supplementary Table 1 describes the codification for each type of adverse event. Secondary outcomes of special interest were anemia, neutropenia (including pancytopenia) and elevation hepatic transaminases. Interruption of treatment for any reason (including due to loss of

follow-up; except pregnancy or disease remission), due to inefficacy and due to adverse events also served as secondary outcomes (see Supplementary Table 2).

Details of data management and quality control are described in Supplementary Text 1. For the present analysis, only the first course of treatment, after patients' inclusion in the cohort, was considered for analysis. A treatment course is defined as a period during which the medication scheme does 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, at the day before the start of a new treatment course, at the moment of death or loss to follow-up, or Nov 19, 2019 (whatever came first).

Statistical analysis

The data were analyzed using and SPSS for Windows, version 20.0 (IBM Corporation, Armonk, NY, USA), and the Survival, MatchIt, and Stddiff packages of R (version 3.3.3, R Foundation for Statistical Computing, Vienna, Austria). The association between categorical variables was tested using Pearson's chi-square test or Fisher's exact test. Variables with a normal distribution were presented as the mean and standard deviation, and the between-group comparisons were performed using Student t test or analysis of variance (ANOVA). Non-normal quantitative variables were presented as the median and interquartile range, and between-group comparisons were performed using the Mann-Whitney or Kruskal-Wallis tests. Incidence-density data (along with 95% confidence intervals) 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 propensity score matched analysis

(PSMA) (35-37). P values less than or equal to 0.05 were considered statistically significant (all

presented P values are 2-tailed). See further details in Supplementary Text 2.

RESULTS

Description of the sample

Out of 2111 patients, 1671 (5348.70 patient-years [PY]) starting follow-up in 1st Jan 2009

or thereafter were included in the analysis (see 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 on treatment with the MTX-LEF combo were more frequently

seronegative, more commonly in use of corticosteroids and less frequently in use of sulfasalazine

and biologic agents than other groups of patients. Only 2 patients received treatment with

cyclosporin (both in the group receiving neither MTX nor LEF). Patients using JAK inhibitor

were taking exclusively tofacitinib. The median duration of follow-up in the entire sample was

2.17 years (interquartile range, 0.96 to 4.59 years) before censoring or the first serious adverse

event. The overall incidence of serious adverse events (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 combo was 1536.6 PY.

Comparison of the MTX-LEF combo with MTX/LEF

The comparison of the incidences and hazards of primary and secondary outcomes

between the MTX-LEF combo 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 adverse events

presented higher incidence with the MTX-LEF combo in relation to therapy with MTX or LEF. Total cardiovascular (univariate analysis) and total infectious events (multivariate analysis) were also more frequent with the MTX-LEF combo. In the multivariate models presented in table 2, antimalarials were significantly protective for SAEs (adj. HR: 0.73, 95% CI: 0.55 to 0.98, P=0.035) and total hepatic adverse events (0.26, 0.09 to 0.74, P=0.012). Sulfasalazine (SSZ) was related to higher hazards of SAEs (adj. HR: 2.35, 1.49 to 3.71, P<0.001), total adverse events (1.60, 1.16 to 2.20, P=0.004), total hematologic events (3.36, 1.16 to 9.75, P=0.026) and total (1.81, 1.18 to 2.76, P=0.006) and serious infections (2.08, 1.06 to 4.06, P=0.033). Biologics/JAK inhibitors were associated with higher hazards of SAEs (adj. HR: 1.49, 1.12 to 1.98, P=0.006), total adverse events (1.61, 1.36 to 1.90, P<0.001), and total (2.10, 1.65 to 2.67, P<0.001) and serious infections (2.53, 1.61 to 3.96, P<0.001).

In an alternative analysis, we compared the hazard of SAE of the MTX-LEF combo with a category representing the use of MTX, adjusting for potential confounding variables (see Supplementary Table 3). Again, there was no significant increase in risk of SAE (adjusted HR: 1.02, 0.77 to 1.36, P=0.890) with MTX plus LEF.

Considering the risk of laboratory abnormalities comparing the MTX-LEF combo with the MTX or LEF group, there were numerically higher incidence of anemia (0.7, 95% CI, 0.4 to 1.2/100 PY, versus 0.4, 0.2 to 0.6/100 PY, respectively) and elevation of hepatic transaminases (0.6, 0.3 to 1.1/100 PY, versus 0.3, 0.1 to 0.5/100 PY, respectively) in the former group. Univariate hazard ratios for the comparisons listed above were 1.91(95% CI: 0.88 to 4.13, P=0.100) and 2.28 (0.95 to 5.48, P=0.065), respectively. The incidence of neutropenia was 0.1 (95% CI, <0.1 to 0.5)/100 PY in MTX plus LEF group comparing to 0.2 (0.1 to 0.4)/100 PY in the MTX or LEF group (HR: 0.74, 0.15 to 3.66, P=0.712). However, these analyses may be

limited by the small number events recorded (anemia, elevation of hepatic transaminases and neutropenia represented only 30, 22 and 10 events, respectively).

MTX-LEF combo versus biologics/JAKi (with MTX or LEF)

Table 3 shows the comparison of the hazards of primary and secondary outcomes between the MTX-LEF combo and the combination of bDMARDs or JAK inhibitor with MTX or LEF (reference category). The patients' features are described in Supplementary Table 4. There was a significant reduction in the hazards of serious adverse events, total and serious infections with the MTX-LEF combo comparing to the reference group. Figure 2 shows the comparison of the cumulative incidence of SAEs between the groups. Comparing exclusively patients on the MTX-LEF combo with those on MTX plus biologics/tofacitinib, similar results were observed (see Supplementary Table 5).

MTX-LEF combo versus MTX plus SSZ

Supplementary Table 6 describes the patients' features and Supplementary Table 7 compares the hazards of SAEs and secondary outcomes of the MTX-LEF combo and the MTX-SSZ combination. A reduction in the hazards of SAEs (adj. HR: 0.33, 0.16 to 0.65, P= 0.002) and total hematologic events (univariate HR: 0.26, 0.08 to 0.90, P=0.033) was observed with the use of MTX plus LEF.

Analysis of drug survival

The comparison of hazard of interruption of treatment is shown in Supplementary Table 8. The MTX-LEF combo was associated with lower hazards of interruption due to adverse events or death (adj. HR: 0.31, 95% CI, 0.17 to 0.58, P<0.001) and for any reason (adj. HR: 0.76,

0.61 to 0.95, P=0.016; see Figure 3) in comparison to bDMARDs/JAKi (with MTX or LEF). There was no difference in the hazard of interruption due to inefficacy (adj. HR: 0.84, 0.62 to 1.12, P=0.237). The MTX-LEF combination was related to lower hazards of therapy interruption for any reason (univariate HR: 0.62, 0.39 to 0.98, P=0.042) and due to adverse events (adj. HR: 0.38, 0.15 to 0.96, P=0.040) in comparison to the MTX-SSZ combo.

MTX plus LEF versus MTX/LEF among patients treated with biologics or JAKi

Considering the relatively large number (n=257) of patients on MTX plus LEF along with biologics/JAKi (MLB/J), we compared these patients with those also using biologics/JAKi, but with MTX or LEF (reference category). Patients' features are described in Supplementary Table 9. Serious adverse events (univ. HR: 1.41, 1.03 to 1.92, P=0.030), total adverse events (adj. HR: 1.21, 1.00 to 1.46, P=0.050) and total cardiovascular events (adj. HR: 2.04, 1.21 to 3.41, P=0.007) presented higher incidence in MLB/J group, while serious infections (univariate HR: 1.50, 0.99 to 2.29, P=0.058) tended occur more frequently in MLB/J group than in the reference category (Supplementary Table 10).

Sensitivity analyses

We performed different sensitivity analyses removing possible preset combinations of MTX plus 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), confirming the results previously presented. A comparison of hazard of SAE between the MTX-LEF combo 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 the Supplementary Figure.

The results obtained with traditional multivariate Cox methods were re-evaluated using PSMA (see the Propensity Score Matched Analysis Supplement), and the results of both types of analysis were very similar.

DISCUSSION

In the present study, the combination of MTX and LEF presented a safety profile comparable to the uncombined use of both drugs. Despite the increased frequency of total adverse events (mainly infections and cardiovascular events), the incidence of serious infections, serious cardiovascular events, and total SAEs was not significantly changed with the combination. Comparing the MTX-LEF combo 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 due to adverse events) was also lower with MTX plus LEF, suggesting that this combination has an acceptable safety profile in RA patients who fail treatment with monotherapy or other combinations of csDMARDs. However, among patients using biologics, 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 randomized controlled trials (RCTs) showing superiority comparing to MTX alone (9) and suggesting equivalence with MTX plus low-dose rituximab (10) in patients failing therapy with methotrexate. 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 RA patients (38). In these 3 RCTs, there was no increase in the risk of serious adverse events

with the MTX-LEF combo (9,10,38). The safety profile of the MTX-LEF combo has also been evaluated in observational (11,12,14-23,25-27,39) and non-controlled experimental studies (24,29,40-43), but most of these studies followed-up patients for less than one year. The largest study up to now is the retrospective cohort based on a healthcare-system database by Cannon et al. (14), including 2048 patients (1415 patient/years) on MTX plus LEF. This study found even a lower incidence of reported adverse events with the MTX-LEF combo in relation to other combinations involving these drugs. On the other hand, Curtis et al. (11) observed a fourfold increase in the hazard of elevation of transaminases greater than or equal to 2 twofold de upper limit of normal (ULN) with MTX ($\geq$ 7,5 mg/day) plus LEF (20 mg/day). 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, have observed higher prevalence ratio of liver silent fibrosis measured by elastography in patients with MTX plus LEF, and correlated it with the cumulative dose of LEF. In our study, the incidence of serious and non-serious hepatic adverse events (including elevation of liver enzymes) was only numerically higher with MTX plus LEF, but the number of events was smaller than expected and conclusions on hepatic safety can not be drawn form our data.

Hematologic adverse events (mainly neutropenia and pancytopenia) are other feared complications related to the combination of MTX and LEF. Pancytopenia has been reported to occur in 1/4000 patients under LEF treatment and in 1/575-822 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 plus 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, while antimalarials protected for SAEs and reduced the incidence of hepatic events. The MTX-SSZ combo tended to

be associated with higher hazard of adverse event-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 recent evidence suggesting low tolerability of SSZ in RA in settings outside clinical trials (6-8).

Our study has several strengths. To the best of our knowledge, this is the largest cohort study (in terms of number of patient/years) of individuals on treatment with MTX plus LEF, and the first to compare its safety with that 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 bias' by comparing only new-onset MTX-LEF combos with novel combinations of biologics/JAKi plus csDMARDs) and confounding bias. The results obtained with traditional multivariate survival analyses were reconfirmed using propensity score matched analyses.

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 less than 6 months of follow-up (whose SAEs could have been retrospectively recorded) did not change the results significantly (see Supplementary Text 3).

Further limitations of this study include the fact that, despite the use of multivariate analysis, unaccounted residual confounding may still impact 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 impact the incidence of adverse events.

Some analyses presented in this article were limited by the reduced number of patients taking

SSZ. The number of patients on non-anti-TNF biologics and JAKi 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 multi-ethnic South American developing country, what may

have impact 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 lab abnormalities should have been reported, and minor hematologic

adverse events may also have been sub-notified.

Conclusions

Our results suggest that the combination of MTX plus LEF may present a relatively good

safety and tolerability profile in comparison to MTX plus SSZ and schemes involving advanced

therapies in RA. Further studies performed in different clinical and socio-demographic settings

are necessary to confirm these findings.

ACKNOWLEGMENTS

REFERENCES

1.   Singh JA, Saag KG, Bridges SL, Jr., Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol 2016;68:1-26.

2.   Smolen JS, Landewé RB, Bijlsma JW, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis 2020;79:685-99.

3.   Mota LM, Kakehasi AM, Gomides AP, Duarte A, Cruz BA, Brenol CV, et al. 2017 recommendations of the Brazilian Society of Rheumatology for the pharmacological treatment of rheumatoid arthritis. Adv Rheumatol 2018;58:2.

4.   Moreland LW, O'Dell JR, Paulus HE, Curtis JR, Bathon JM, St Clair EW, et al. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the treatment of Early Aggressive Rheumatoid Arthritis Trial. Arthritis Rheum 2012;64:2824-35.

5.   O'Dell JR, Mikuls TR, Taylor TH, Ahluwalia V, Brophy M, Warren SR, et al. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med 2013;369:307-18.

6.   Gomides APM, de Albuquerque CP, Santos ABV, Amorim RBC, Bértolo MB, Júnior PL, et al. Causes of synthetic disease-modifying drug discontinuation in rheumatoid arthritis: Data from a large real-life cohort. PLoS One 2019;14:e0213219.

7.   Erhardt DP, Cannon GW, Teng CC, Mikuls TR, Curtis JR. Low Persistence Rates in Patients With Rheumatoid Arthritis Treated With Triple Therapy and Adverse Drug Events Associated With Sulfasalazine. Arthritis Care Res (Hoboken) 2019;71:1326-35.

8. Curtis JR, Palmer JL, Reed GW, Greenberg J, Pappas DA, Harrold LR, et al. Real-World Outcomes Associated with Triple Therapy versus TNFi/MTX Therapy. Arthritis Care Res (Hoboken) 2020 [Ahead of print].

9. Kremer JM, Genovese MC, Cannon GW, Caldwell JR, Cush JJ, Furst DE, et al. Concomitant leflunomide therapy in patients with active rheumatoid arthritis despite stable doses of methotrexate. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 2002;137:726-33.

10. Wijesinghe H, Galappatthy P, de Silva R, Seneviratne SL, Saravanamuttu U, Udagama P, et al. Leflunomide is equally efficacious and safe compared to low dose rituximab in refractory rheumatoid arthritis given in combination with methotrexate: results from a randomized double blind controlled clinical trial. BMC Musculoskelet Disord 2017;18:310.

11. Curtis JR, Beukelman T, Onofrei A, Cassell S, Greenberg JD, Kavanaugh A, et al. Elevated liver enzyme tests among patients with rheumatoid arthritis or psoriatic arthritis treated with methotrexate and/or leflunomide. Ann Rheum Dis 2010;69:43-7.

12. Lee SW, Park HJ, Kim BK, Han KH, Lee SK, Kim SU, et al. Leflunomide increases the risk of silent liver fibrosis in patients with rheumatoid arthritis receiving methotrexate. Arthritis Res Ther 2012;14:R232.

13. McEwen J, Purcell PM, Hill RL, Calcino LJ, Riley CG. The incidence of pancytopenia in patients taking leflunomide alone or with methotrexate. Pharmacoepidemiol Drug Saf 2007;16:65-73.

14. Cannon GW, Holden WL, Juhaeri J, Dai W, Scarazzini L, Stang P. Adverse events with disease modifying antirheumatic drugs (DMARD): a cohort study of leflunomide compared with other DMARD. J Rheumatol 2004;31:1906-11.

15. Alves JA, Fialho SC, Morato EF, Castro GR, Zimmermann AF, Ribeiro GG, et al. Liver toxicity is rare in rheumatoid arthritis patients using combination therapy with leflunomide and methotrexate. Rev Bras Reumatol 2011;51:141-4.

16. Dendooven A, De Rycke L, Verhelst X, Mielants H, Veys EM, De Keyser F. Leflunomide and methotrexate combination therapy in daily clinical practice. Ann Rheum Dis 2006;65:833-4.

17. Antony T, Jose VM, Paul BJ, Thomas T. Efficacy and safety of leflunomide alone and in combination with methotrexate in the treatment of refractory rheumatoid arthritis. Indian J Med Sci 2006;60:318-26.

18. Chopra A, Saluja M, Lagu-Joshi V, Sarmukadam S. Leflunomide (Arava) is a useful DMARD in Indian (Asian) patients: a clinic-based observational study of 1-year treatment. Clin Rheumatol 2008;27:1039-44.

19. Kaul A, O'Reilly DT, Slack RK, Collins D, Walmsley J, Duke O, et al. Tolerability of methotrexate and leflunomide combination therapy for inflammatory arthritis in routine clinical practice: results of a four-centre study. Rheumatology (Oxford) 2008;47:1430-1.

20. Cubides MF, Fernandez Avila DG, Santos Moreno P, Jaimes D, Reyes E, Londoño J, et al. Use of leflunomide plus methotrexate combination in a group of patients with active rheumatoid arthritis in colombia. It's not so bad! Ann Rheum Dis 2010;69 (Suppl. 3):684.

21. Hensley G, Karpouzas GA. Good long-term tolerance of methotrexate plus leflunomide in minority patients with rheumatoid arthritis (RA). Ann Rheum Dis 2010;69 (suppl. 3):216.

22. Ahmad NM, Farman S, Saeed MA, Hameed R, Umair M, Ghafoor E. Leflunomide in Pakistani patients with rheumatoid arthritis: prospective study in daily rheumatology practice. Int J Rheum Dis 2011;14:48-54.

23.   Gupta R, Bhatia J, Gupta SK**.** Risk of hepatotoxicity with add-on leflunomide in rheumatoid arthritis patients. Arzneimittelforschung 2011;61:312-6.

24.   Londono J, Santos AM, Santos PI, Cubidez MF, Guzman C, Valle-Oñate R**.** Therapeutic efficacy and safety of methotrexate + leflunomide in Colombian patients with active rheumatoid arthritis refractory to conventional treatment. Rev Bras Reumatol 2012;52:837-45.

25.   Bird P, Griffiths H, Tymms K, Nicholls D, Roberts L, Arnold M, et al. The SMILE study -- safety of methotrexate in combination with leflunomide in rheumatoid arthritis. J Rheumatol 2013;40:228-35.

26.   Abasolo L, Leon L, Rodriguez-Rodriguez L, Tobias A, Rosales Z, Maria Leal J, et al. Safety of disease-modifying antirheumatic drugs and biologic agents for rheumatoid arthritis patients in real-life conditions. Semin Arthritis Rheum 2015;44:506-13.

27.   Hodkinson B, Magomero KR, Tikly M**.** Combination leflunomide and methotrexate in refractory rheumatoid arthritis: a biologic sparing approach. Ther Adv Musculoskelet Dis 2016;8:172-9.

28.   Titton DC, Silveira IG, Louzada-Junior P, Hayata AL, Carvalho HM, Ranza R, et al. Brazilian biologic registry: BiobadaBrasil implementation process and preliminary results. Rev Bras Reumatol 2011;51:152-60.

29.   Brazilian Society of Rheumatology. Manual BiobadaBrasil versão 2.1. Accessed at https://biobadaser.ser.es/biobadamerica/Brasil/cgi-bin/upload/archivo.aspx?id=10 on Apr 29, 2020.

30.   Carmona L, de la Vega M, Ranza R, Casado G, Titton DC, Descalzo M, et al. BIOBADASER, BIOBADAMERICA, and BIOBADADERM: safety registers sharing commonalities across diseases and countries. Clin Exp Rheumatol 2014;32:S-163-7.

31. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.

32. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569-81.

33. Brazilian Society of Rheumatology. [Criteria for patient inclusion – BiobadaBrasil]. Accessed at https://www.reumatologia.org.br/biobadabrasil/criterios-para-inclusao-de-pacientes-biobadabrasil/ on May 4, 2020.

34. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Medical Dictionary for Regulatory Activities (MedDRA). Accessed at http://www.meddra.org on Apr 29, 2020.

35. Austin PC. A comparison of 12 algorithms for matching on the propensity score. Stat Med 2014;33:1057-69.

36. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat 2011;10:150-61.

37. Ho DE, Imai K, King G, Stuart EA. MatchIt: Nonparametric Preprocessing for Parametric Causal Inference. J Stat Softw 2011;42:1-28.

38. Stouten V, Westhovens R, Pazmino S, De Cock D, Van der Elst K, Joly J, et al. Effectiveness of different combinations of DMARDs and glucocorticoid bridging in early rheumatoid arthritis: two-year results of CareRA. Rheumatology (Oxford) 2019;58:2284-94.

39.   Ding CZ, Yao Y, Feng XB, Fang Y, Zhao C, Wang Y. Clinical analysis of chinese

        patients with rheumatoid arthritis treated with leflunomide and methotrexate combined

        with different dosages of glucocorticoid. Curr Ther Res Clin Exp 2012;73:123-33.

40.   Weinblatt ME, Kremer JM, Coblyn JS, Maier AL, Helfgott SM, Morrell M, et al.

        Pharmacokinetics, safety, and efficacy of combination treatment with methotrexate and

        leflunomide in patients with active rheumatoid arthritis. Arthritis Rheum 1999;42:1322-8.

41.   Xiang N, Li XM, Zhang MJ, Zhao DB, Zhu P, Zuo XX, et al. Total glucosides of paeony

        can reduce the hepatotoxicity caused by Methotrexate and Leflunomide combination

        treatment of active rheumatoid arthritis. Int Immunopharmacol 2015;28:802-7.

42.   Samreen S, Salim B, Nasim A. Safety of methotrexate and leflunomide as a combination

        therapy in patients of rheumatoid arthritis. Pak Armed Forces Med J 2017;67:988-95.

43.   Kremer J, Genovese M, Cannon GW, Caldwell J, Cush J, Furst DE, et al. Combination

        leflunomide and methotrexate (MTX) therapy for patients with active rheumatoid arthritis

        failing MTX monotherapy: open-label extension of a randomized, double-blind, placebo

        controlled trial. J Rheumatol 2004;31:1521-31.

FIGURE LEGENDS

Figure 1. Flow diagram describing the enrollment of patients.

Figure 2. Kaplan-Meier curves comparing the cumulative incidence of serious adverse events between patients taking MTX plus LEF and those taking bDMARDs/JAKi with MTX ou LEF. The vertical traces represent censored patients. CI: confidence interval; MTX: methotrexate; LEF: leflunomide; bDMARDs: biologic disease modifying anti-rheumatic drugs; JAKi: janus kinase inhibitor.

Figure 3. Kaplan-Meier curves comparing the survival of treatment course between patients taking MTX plus LEF and those using bDMARDs/JAKi (with MTX ou LEF). The vertical traces represent censored patients. CI: confidence interval; MTX: methotrexate; LEF: leflunomide; bDMARDs: biologic disease modifying anti-rheumatic drugs; JAKi: janus kinase inhibitor.

Table 1. Baseline clinical and demographic features of the patients followed-up in the cohort. The medications reported in the table represent those used concurrently during the first treatment course. Data are presented as number (percentage) of patients, except when indicated otherwise.

	Neither MTX nor LEF (n=156)	MTX (n= 766)	LEF (n=297)	MTX plus LEF (n=452)	P Value*
Female	125 (80.1)	651 (85.0)	261 (87.9)	393 (86.9)	0.115
Age (years) – mean (SD)	54.7 (14.2)	50.7 (12.0)	52.2 (11.8)	50.7 (11.6)	0.001
Disease duration (years) – 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** – mean (SD)	5.15 (1.49)	5.24 (1.57)	5.20 (1.41)	5.08 (1.36)	0.330
Current smoking	15 (9.6)	115 (15.0)	38 (12.8)	79 (17.5)	0.076

History of malignancy	4 (2.6)	8 (1.0)	4 (1.3)	6 (1.3)	0.470
Diabetes	24 (15.4)	86 (11.2)	47 (15.8)	58 (12.8)	0.169
Hypertension	61 (39.1)	271 (35.4)	131 (44.1)	176 (38.9)	0.068
Hypercholesterolemia	27 (17.3)	82 (10.7)	50 (16.8)	71 (15.7)	0.009
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)	0.939
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)	0.580
COPD	2 (1.3)	14 (1.8)	9 (3.0)	12 (2.7)	0.497
Heart failure	2 (1.3)	4 (0.5)	2 (0.7)	4 (0.9)	0.580
Corticosteroid	117 (75.0)	602 (78.6)	232 (78.1)	380 (84.1)	0.037
Hydroxychloroquine or chloroquine	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***	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 year – mean (SD)	2013.7 (3.0)	2012.4 (3.1)	2013.1 (3.1)	2012.1 (2.7)	<0.001

*Pearson chi-square, Fisher's exact test, analysis of variance or Kruskal-Wallis test according to the nature and distribution of data. **Data on DAS28 of 7 patients were not available. ***Other biologics are abatacept, rituximab or tocilizumab. MTX: methotrexate; LEF: leflunomide; SD: standard deviation; IQR: interquartile range; RA: rheumatoid arthritis; RF: rheumatoid factor; CCP: cyclic citrullinated peptide; DAS28: Disease Activity Score in 28 joints; COPD: chronic obstructive pulmonary disease; TNF: tumor necrosis factor; JAK: Janus kinase.

Table 2. Results of Cox proportional hazards models testing the association of the MTX-LEF combo with adverse events in comparison to a group representing use of MTX or LEF.

Type of adverse event (number of events)	MTX-LEF combo (n=452) Rate per 100 PY (95% CI)	MTX or LEF (n=1063) Rate per 100 PY (95% CI)	Hazards ratios (95% CI), P value	
			Crude analysis*	Adjusted for covariates*†
Total serious adverse events (298)	5.4 (4.4 to 6.6)	5.4 (4.7 to 6.2)	1.01 (0.78 to 1.31), P=0.915	1.00 (0.76 to 1.31), P=0.984
Fatal adverse events (26)	0.5 (0.2 to 0.9)	0.4 (0.2 to 0.6)	1.27 (0.53 to 3.02), P=0.593	1.23 (0.46 to 3.30), P=0.681
Any adverse event (854)	26.5 (23.8 to 29.4)	22.2 (20.6 to 24.0)	1.16 (1.00 to 1.34), P=0.057	1.22 (1.04 to 1.42), P=0.013
Cardiovascular‡ Serious (40)	0.8 (0.4 to 1.3)	0.6 (0.4 to 0.9)	1.30 (0.66 to 2.58), P=0.451	1.04 (0.49 to 2.21), P=0.924
Total (106)	2.5 (1.9 to 3.4)	1.6 (1.3 to 2.1)	1.56 (1.04 to 2.32), P=0.030	1.33 (0.87 to 2.03), P=0.181

Infections	Serious (144)	2.6 (1.9 to 3.5)	2.3 (1.9 to 2.9)	1.16 (0.80 to 1.67), P=0.437	1.24 (0.84 to 1.82), P=0.276
	Total (458)	10.8 (9.2 to 12.6)	9.5 (8.5 to 10.6)	1.14 (0.93 to 1.40), P=0.212	1.26 (1.02 to 1.56), P=0.029
Hepatic‡	Serious (8)	0.2 (0.06 to 0.5)	0.1 (0.05 to 0.3)	ND	ND
	Total (42)	0.9 (0.5 to 1.5)	0.6 (0.4 to 0.9)	1.48 (0.77 to 2.83), P=0.241	1.44 (0.72 to 2.85), P=0.299
Hematologic	Serious (12)	0.2 (0.1 to 0.6)	0.2 (0.1 to 0.4)	1.51 (0.43 to 5.35), P=0.523	ND
	Total (49)	1.0 (0.6 to 1.6)	0.8 (0.5 to 1.1)	1.28 (0.69 to 2.36), P=0.437	1.17 (0.62 to 2.21), P=0.628
Respiratory tract‡	Serious (16)	0.2 (0.1 to 0.6)	0.3 (0.1 to 0.5)	0.87 (0.27 to 2.78), P=0.816	ND
	Total (57)	0.8 (0.5 to 1.4)	1.1 (0.8 to 1.5)	0.91 (0.49 to 1.70), P=0.769	1.05 (0.55 to 2.00), P=0.878

| Gastrointestinal‡ | Serious (15) | 0.2 (0.1 to 0.6) | 0.3 (0.1 to 0.5) | 0.89 (0.28 to 2.84), P=0.842 | ND |
| | Total (102) | 1.9 (1.3 to 2.6) | 1.7 (1.3 to 2.2) | 1.09 (0.71 to 1.68), P=0.691 | 1.06 (0.68 to 1.67), P=0.782 |

* These analyses include 1671 patients, since 156 patients taking neither MTX nor LEF are accounted for in multivariate analysis.

†Adjusted also for age, baseline DAS28, disease duration, gender, current smoking, seropositivity for RF 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, hypercholesterolemia, osteoporosis, hepatitis B and C. ‡Excluding infections of any kind. MTX: methotrexate; LEF: leflunomide; CI: confidence interval; PY: Patient-years; ND: not done due to small number of events (<10 for crude analysis and <20 for multivariate analysis); RF: rheumatoid factor; CCP: cyclic citrullinated peptide; COPD: chronic obstructive pulmonary disease.
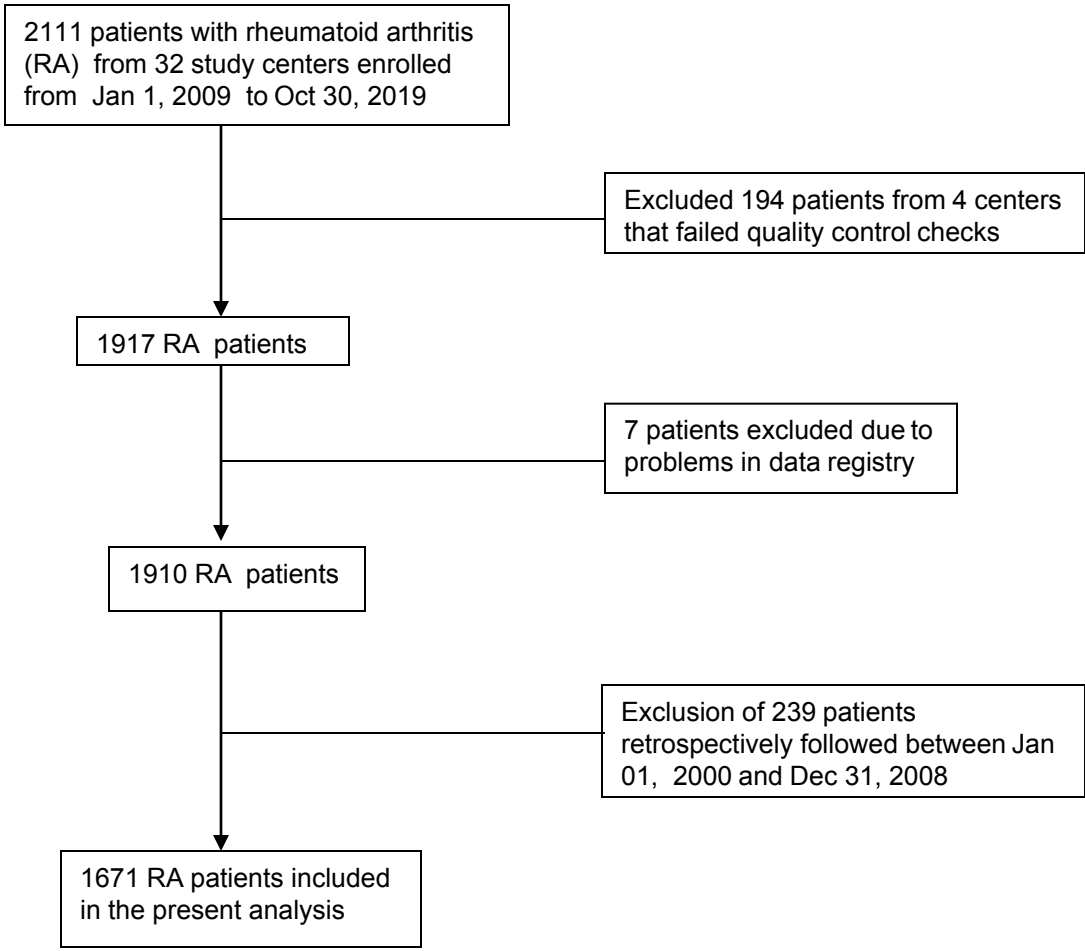
Table 3. Results of Cox proportional hazards models comparing the hazard of adverse events of the MTX-LEF combo versus biologic agents/JAK inhibitor (combined with either MTX or LEF).
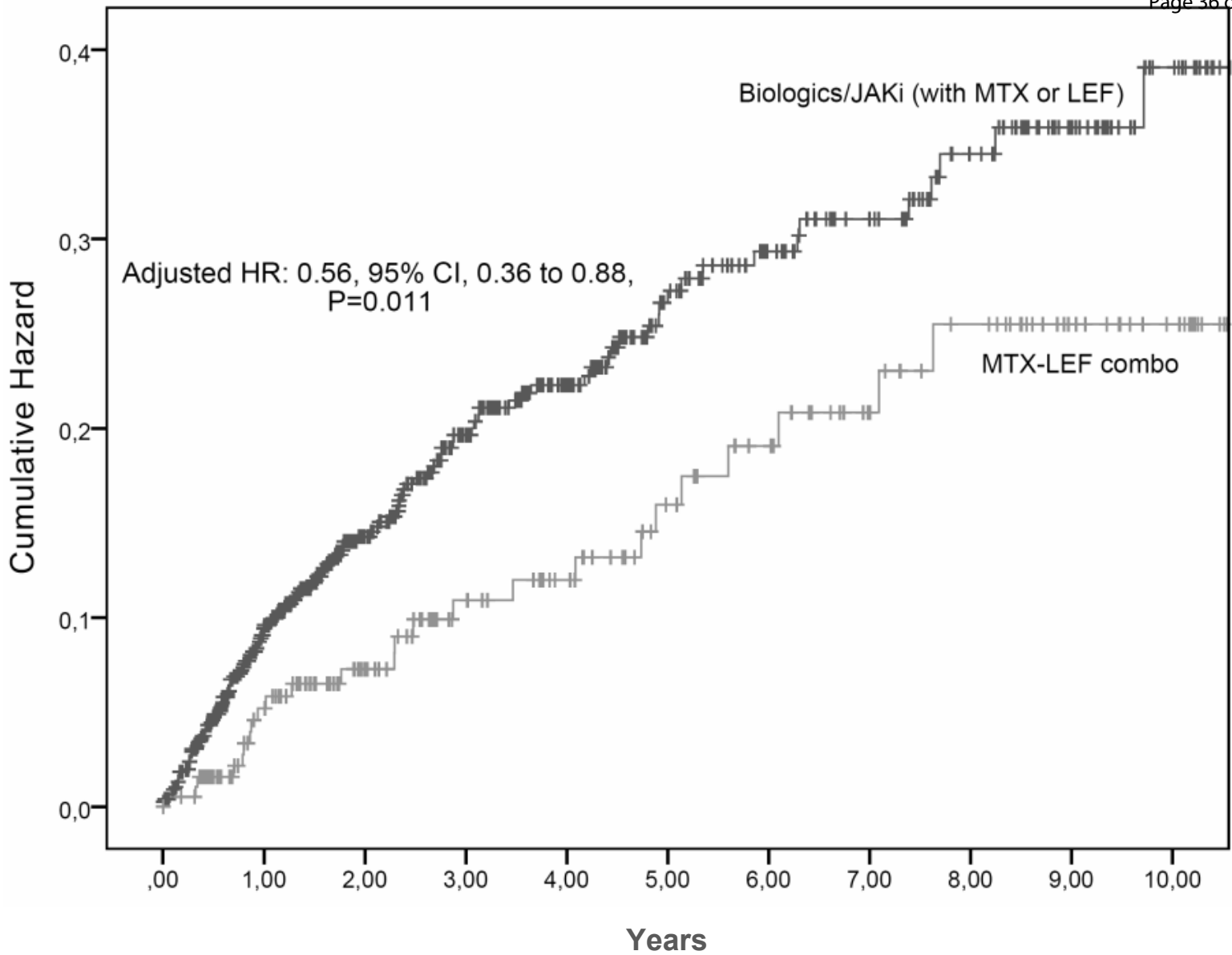
Type of adverse event (number of events)	MTX-LEF combo (n=195) Rate per 100 PY (95% CI)	Biologic agents/JAK inhibitor (with MTX or LEF) (n=775) Rate per 100 PY (95% CI)	Hazards ratios (95% CI), P value Crude analysis*	Adjusted for covariates*†
Total serious adverse events (156)	3.0 (2.1 to 4.5)	5.5 (4.7 to 6.5)	0.61 (0.40 to 0.94), P=0.024	0.56 (0.36 to 0.88), P=0.011
Fatal adverse events (11)	0.3 (0.1 to 1.0)	0.3 (0.2 to 0.6)	1.1 (0.29 to 4.18), P=0.887	ND
Any adverse event (509)	19.7 (16.6 to 23.5)	25.7 (23.7 to 28.0)	0.83 (0.66 to 1.03), P=0.089	0.80 (0.64 to 1.00), P=0.055
Cardiovascular‡ Serious (16)	0.6 (0.2 to 1.4)	0.4 (0.2 to 0.8)	1.42 (0.49 to 4.11), P=0.517	ND

	Total (52)	1.8 (1.1 to 2.9)	1.5 (1.1 to 2.0)	1.26 (0.69 to 2.30), P=0.454	0.85 (0.44 to 1.64), P=0.621
Infections	Serious (78)	1.2 (0.7 to 2.3)	2.7 (2.1 to 3.4)	0.53 (0.28 to 1.00), P=0.050	0.48 (0.25 to 0.94), P=0.031
	Total (282)	7.2 (5.5 to 9.4)	11.7 (10.4 to 13.2)	0.70 (0.51 to 0.94), P=0.020	0.70 (0.51 to 0.96), P=0.027
Hepatic‡	Serious (2)	0.0 (NA)	0.1 (<0.1 to 0.3)	ND	ND
	Total (23)	0.9 (0.5 to 1.9)	0.6 (0.4 to 1.0)	1.72 (0.73 to 4.07), P=0.217	2.03 (0.80 to 5.12), P=0.136
Hematologic	Serious (4)	0.2 (0.1 to 0.9)	0.1 (<0.1 to 0.3)	ND	ND
	Total (29)	1.1 (0.6 to 2.0)	0.8 (0.5 to 1.2)	1.40 (0.64 to 3.09), P=0.400	1.76 (0.75 to 4.11), P=0.193
Respiratory tract‡	Serious (9)	0.2 (0.1 to 0.9)	0.3 (0.1 to 0.6)	ND	ND
	Total (31)	0.7 (0.3 to 1.5)	1.0 (0.7 to 1.4)	0.74 (0.30 to 1.81), P=0.508	0.91 (0.34 to 2.41), P=0.852
Gastrointestinal‡	Serious (7)	0.1 (<0.1 to 0.8)	0.2 (0.1 to 0.5)	ND	ND

	Total (59)	1.8 (1.1 to 2.9)	1.7 (1.3 to 2.3)	1.02 (0.56 to 1.84), P=0.954	1.19 (0.63 to 2.25), P=0.590

* These analyses include 970 patients. †Adjusted also for age, baseline DAS28, disease duration, gender, current smoking, seropositivity for RF 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, hypercholesterolemia, osteoporosis, hepatitis B and C. ‡Excluding infections of any kind. MTX: methotrexate; LEF: leflunomide; CI: confidence interval; PY: Patient-years; ND: not done due to small number of events (<10 for crude analysis and <20 for multivariate analysis); RF: rheumatoid factor; CCP: cyclic citrullinated peptide; COPD: chronic obstructive pulmonary disease; NA: not applicable.
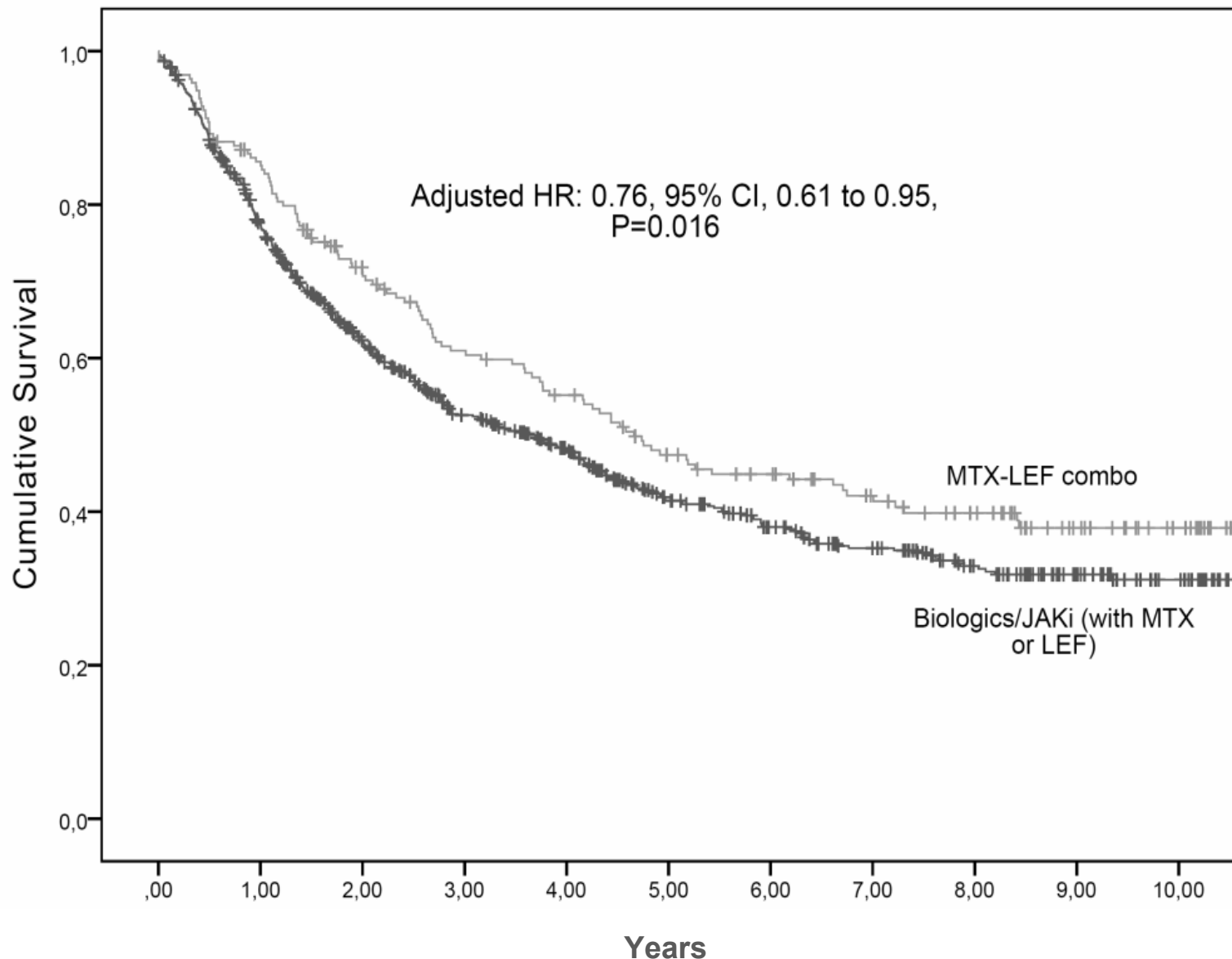
2111 patients with rheumatoid arthritis (RA) from 32 study centers enrolled from Jan 1, 2009 to Oct 30, 2019

Excluded 194 patients from 4 centers that failed quality control checks

1917 RA patients

7 patients excluded due to problems in data registry

1910 RA patients

Exclusion of 239 patients retrospectively followed between Jan 01, 2000 and Dec 31, 2008

1671 RA patients included in the present analysis

Number at risk

Biologics/JAKi	775	564	388	285	223	158	128	102	77	49	26
MTX-LEF combo	195	160	123	98	86	69	59	47	39	27	19

Adjusted HR: 0.76, 95% CI, 0.61 to 0.95, P=0.016

MTX-LEF combo

Biologics/JAKi (with MTX or LEF)

Cumulative Survival

Years

Number at risk

Biologics/JAKi	775	571	415	311	250	180	146	120	89	57	34
MTX-LEF combo	195	164	127	106	94	77	69	57	48	31	20

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

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.