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SAFETY OF THE METHOTREXATE-LEFLUNOMIDE COMBINATION IN THE BRAZILIAN REGISTRY OF BIOLOGICAL THERAPIES IN RHEUMATIC DISEASES (BIOBADABRASIL)

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BACKGROUND

The combination of methotrexate (MTX) with leflunomide (LEF), despite being effective in the therapy of rheumatoid arthritis (RA)[1], has not been widely accepted[2,3]. In spite of evidence that the MTX-LEF combination is generally safe [1,4,5], the relatively small number of patients and treatment courses have not permitted firm conclusions. Our objective was to evaluate the safety of the combination MTX-LEF in Brazilian patients with RA included in BiobadaBrasil.

MATERIALS AND METHODS

BiobadaBrasil is a multicentric prospective cohort involving patients with rheumatic diseases who started their first biologic or a synthetic disease modifying anti-rheumatic drug (DMARD)[6]. This analysis includes RA (2010 criteria) patients recruited from Jan 2009 to Aug 2018, followed-up for one or multiple courses of treatment until censoring (latest date, September 03, 2018) or occurrence of the outcome of interest.

The primary outcome was the incidence of any serious AE (SAE). Secondary outcomes were infectious, non-mycobacterial pulmonary infectious, hepatic, hematologic and cardiovascular SAE. Multivariate Cox proportional hazards models (with DMARDs included as time-varying covariates) were used to estimate hazard ratios (HR) and 95% confidence intervals (CI); analyses were performed with the Survival package of R.

RESULTS

Sample: 2055 RA patients, female=85.1%, median disease duration=6.02 yrs; mean (SD) age=50.3 (12.1) yrs; mean (SD) DAS28=5.3 (3.1); seronegative RA=14.1%; median follow-up duration=3.9 yrs. In total, 565 patients received 664 courses of the MTX-LEF combination (median duration, 2.5 years/course; 2209 person-years). The incidence of SAE was 4.75/100 patient-year in the entire sample. There was no significant increase in the risk of any of the outcomes with the use of combined therapy (table 1) comparing with methotrexate (without leflunomide). The use of antimalarials was associated with reduced risk of SAE (adjusted HR=0.62, 95% CI 0.48 to 0.79, P<0.001), while sulfasalazine (adj. HR= 1.78, 1.18 to 2.68, P=0.006) and biologic DMARDs/tofacitinib (adj. HR= 1.67, 1.31 to 2.12, P<0.001) increased the risk of SAE.

CONCLUSION

BIOBADABRASIL results suggest that the combination of methotrexate and leflunomide is safe in the treatment of RA.

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[5] Rev Bras Reumatol 2011; 51: 141/51:152.