TOFACITINIB MONOTHERAPY OR COMBINED WITH METHOTREXATE IN PATIENTS WITH RHEUMATOID ARTHRITIS SHOW SIMILAR RETENTION OVER FOUR YEARS. REPORT FROM RHUMADATA®

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Background: Since the introduction of biologic agents around the turn of the century, the scientific evidence shows that the majority of agents, independent of the therapeutic target, have a better outcome when used in combination with methotrexate (MTX). In 2014, tofacitinib (TOFA), an agent targeting Janus kinase 1 and 3, has reached the Canadian market with data showing that the combination of MTX may be necessary [1,2].

Objectives: To evaluate the efficacy and retention rate of TOFA in real-world patients with rheumatoid arthritis (RA).

Methods: Two cohorts of patients prescribed TOFA was created. The first cohort was formed of patients who were receiving MTX concomitantly with TOFA (COMBO) and the other of patients using TOFA in monotherapy (MONO). MONO patients either never use MTX or were prescribed MTX post-TOFA initiation for at most 20% of the time they were on TOFA. COMBO patients received MTX at the time of TOFA initiation or were prescribed MTX post-TOFA initiation for at least 80% of the time. For all those patients, baseline demographic data and disease activity score and HAQ-DI were compared from the initiation of TOFA to the last visit. Time to medication discontinuation was extracted, and survival was estimated using Kaplan-Meier calculation for MONO and COMBO cohorts.

Results: Overall, 194 patients were selected. Most were women (83%) on average younger than the men (men: 62.6 ± 11.0 years vs. women: 56.9 ± 12.1 years, p-value=0.0130). The patient's assessments of global disease activity, pain, and fatigue were respectively 5.0 ± 2.7, 5.2 ± 2.9, 5.1 ± 3.1 in the COMBO group and 6.2 ± 2.5, 6.5 ± 2.6, 6.3 ± 2.8 in the MONO group. Besides the type of polymorphism, data on the activity of the disease were analyzed. DAS28 and SDAI defined the level of disease activity and HAQ-DI defined the level of disability. In the COMBO group, the average DAS28 at the start of the MTX income, of the BT, and in the inclusion visit which is 23.9 ± 9.4 and 25.2 ± 11.5, p-value=0.5546. Average changes in SDAI were -13.4 ± 15.5 (COMBO) and -8.9 ± 13.5 (MONO), p-value=0.1515, and changes in HAQ-DI were -0.21 ± 0.63 and -0.26 ± 0.74, p-value=0.6112. At treatment initiation, DAS28(4)ESR were 4.4 ± 1.4 (COMBO) and 4.6 ± 1.3 (MONO), p-value=0.9815, with respective average changes of -1.06 ± 0.27 and -0.70 ± 1.96, p-value=0.2852. The Kaplan-Meier analysis demonstrated that the COMBO and MONO retention curves were not statistically different (log-rank p-value=0.9318).

Conclusion: Sustainability of TOFA in MONO or COMBO are not statistically different as are the changes in DAS28(4)ESR and SDAI. Despite this result, some patients may still benefit from combination with MTX.

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EVALUATION OF THE ASSOCIATION OF ALLELES OF INTOLERANCE RISK TO METOTREXATE IN RHEUMATOID ARTHRITIS PATIENTS UNDER TREATMENT WITH BIOLOGIC THERAPIES

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Background: Metotrexate (MTX) is the first-line treatment for rheumatoid arthritis (RA) both in monotherapy and in combination with biologic disease-modifying antirheumatic drugs (bDMARDs), it usually well tolerated but AEs may appear that causing toxicity that requires suspension of the treatment

Objectives: Determine the prevalence of certain polymorphisms among patients that receive bDMARD in monotherapy or in combination with MTX to confirm its relevance as biomarkers of intolerance. Evaluate the influence of certain polymorphisms in the effectiveness of monotherapy or combined treatment in patients, through"Disease Activity Score 28" (DAS28) and other with only bDMARD (controls). All of them had been or were currently treated with MTX, remained with stable doses of bDMARD, and had a DNA sample stored before the inclusion in the study.

Methods: Retrospective observational multicentric study (University Hospital Complex, Granada, Carlos de Haya Hospital, Malaga and University Hospital Reina Sofia, Cordoba), of cases-control of 227 patients with RA (criteria ACR/EULAR), of which 120 received MTX and bDMARD combined therapy (cases) and other with only bDMARD (controls). All of them had been or were currently treated with MTX, remained with stable doses of bDMARD, and had a DNA sample stored before the inclusion in the study.

Results: An analysis was carried out on 227 patients (120 cases and 107 controls) with an average age of 60 (12,1) being women 78,4%, with a time of evolution since diagnosis of 14,84 (7,78) years 48,9% registered adverse events (AE) MTX related, mainly gastrointestinal, hepatobiliary and skin-subcutaneous tissue. The percentage of AE appearance was superior in the monotherapy group than in the group with combined therapy.

Besides the type of polymorphism, data on the activity of the disease were analyzed (DAS28VSG, DAS28PCR, SDAI, CDAI, at the start of the MTX income, of the BT, and in the inclusion visit

A descriptive and comparative study was carried out on all that and afterwards an assessment was made through a multiple logistic regression analysis (MLR) on the risk of intolerance to MTX.

Results: An analysis was carried out on 227 patients (120 cases and 107 controls) with an average age of 60 (12,1) being women 78,4%, with a time of evolution since diagnosis of 14,84 (7,78) years 48,9% registered adverse events (AE) MTX related, mainly gastrointestinal, hepatobiliary and skin-subcutaneous tissue. The percentage of AE appearance was superior in the monotherapy group than in the group with combined therapy.
The most prevalent polymorphism (84.6% (IC95%: 84.09%-85.11%)) and in cases (86.0% (IC95%: 79.43%-92.57%)) was homozygous CC (ITPase-c94a); in controls homozygous GG (GGH-T401C) (87.5% (IC95%: 81.95%-93.42%). There were no significant differences in the parameters of activity between groups, in both, patients were best basally controlled than at the start of the MTX income and/or bDMARD. Being homozygous-AA for the DHFR gene was significantly associated (p<0.05) with the appearance of AE (none of the 4 homozygous AA patients for that gene had AE).

In MLR, homozygous GG (ref. heterozygous AG) in polymorphism GGH-T401C, being homozygous CC (ref. heterozygous TC) in polymorphism ABC22-C24T and PCR (mg/dl) at the start of bDMARD resulted independent predictive factors of MTX intolerance. Conclusion: Polymorphisms T401C for the GGH gene and C24T for the ABC22 gene and PCR at the start of the bDMARD resulted independent predictive factors of MTX intolerance.

...significant result (p<0.05) between groups was found. The adherence of 84.23% (12.45%-100%, median adherence 94.29%). Only 9.09% (n=3) of the patients were better basally controlled than at the start of the MTX income and/or bDMARD. Significant differences (p<0.05) involving MTX adherence and its development may be influenced by MTX adherence, thereby promoting protegerin, the main regulators of bone metabolism, are involved in osteoblasts/osteoclasts balance in inflammatory disease, such as Rheumatoid Arthritis (RA). Janus kinase (JAK) inhibitors (baricitinib and tofacitinib) can reduce the progression of structural damage in patients with moderate to severe RA. Previous studies suggest a link between JAK inhibition, production of RANKL and osteoclastogenesis.1,2 Objectives: To investigate the effect of baricitinib on RANKL serum concentration in unselected RA patients.

Methods: Patients affected by RA according to 2010 ACR criteria, starting treatment with baricitinib as clinically indicated, were consecutively enrolled. Demographic, clinical and laboratory data were collected at baseline (T0) and after three months of therapy (T3). RANKL serum concentration was analyzed by ELISA at the same timepoints. All patients underwent ultrasound (US) examination at T0 and T3. According to OMERACT definition, the presence of synovial effusion, hypertrophy and power Doppler were assessed and scored on a semi-quantitative scale (0=absent, 1=mild, 2=moderate, 3=severe), obtaining a total US score (0-198), representing the joint inflammatory status (15); erosions were registered. Data were expressed as median (interquartile range); Mann-Whitney and Spearman tests were performed for comparisons and p values <0.05 were considered statistically significant.

Results: We prospectively followed up 33 RA patients starting treatment with baricitinib [M/F 8/25; age 58(9) years; disease duration 165(150) months; 22/33 (67%) ACPA-anti-citrullinated protein antibody positive; 24/33 patients (73%) RF-Rheumatoid factor positive]. After three months of therapy we observed a significant reduction of DAS28 CRP, CDAI and SDAI compared to baseline (p<0.0001). The US inflammatory score showed a significant improvement at T3 (p<0.0001). The serum concentration of RANKL showed a significant decrease after three months of therapy from 44 (25.9) to 27.5 (35.3) pg/ml, p=0.0256 (Figure 1). While in 67% of patients RANKL decreased after treatment, in 33% of patients no decrease or an increase of RANKL was detected. Those patients showing an increase of RANKL had similar DAS28 CCRP, CDAI, but had significantly less swollen joints, compared to those in which RANKL decreased (p=0.0364). At baseline, the concentration of RANKL significantly correlated with the swollen joint count (p=0.0117) and ESR (p=0.0482), but not with DAS28 CCRP, CDAI nor with the US inflammatory score. Nevertheless, the reduction of RANKL was not significantly associated with the achievement of low disease/remission after three months of treatment, with ACPA/RF positivity or the presence of erosions detected by US.

Conclusion: This is the first study demonstrating that baricitinib reduces in vivo the serum levels of RANKL, regardless the correlation with disease activity reduces. The discrepancy between the levels of RANKL and the clinical response is in line with previous data in the literature, demonstrating that, under treatment with anti-TNF and anti-IL-1, the decrease of RANKL did not

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