Background: In refractory rheumatoid arthritis (RA), adding other classic synthetic disease-modifying antirheumatic drugs (csDMARDs) such as leflunomide (LFN) to methotrexate (MTX) is one suitable option. Yet, there are safety concerns. LFN interference with Wnt signaling pathway has been reported in other arthritis. This is associated with subchondral bone erosion in RA. Dickkopf-1 (DKK-1) was shown to be a major regulator of joint remodeling, which is associated with subchondral bone erosion in RA. Dickkopf-1 (DKK-1) so; this relationship may be a therapeutic point of interest.

Current therapies used to treat RA are not able to effectively repair damaged joints. To assess the effectiveness and safety of adding LFN to MTX and to evaluate the predictors of drug retention, toxicity and inefficacy. To assess the effectiveness and safety of adding LFN to MTX and to evaluate the predictors of drug retention, toxicity and inefficacy.

Methods: A retrospective clinical record review of adult RA patients followed on our rheumatology department in whom LFN was added to MTX was done.

Results: In total, 77 patients were included, 66.20% females, with a mean age of 56±11 years old. There was a significant reduction of DAS28 only after 3 months of therapy (ΔDAS28 = 1.58±1.17). However, during a median follow up time of 64 (IQR 39-83) months, 58.4% of patients needed to change treatment strategy, 66.7% due to toxicity (median time to toxicity 13 months, IQR 2-16) and 33.33% due to inefficacy (median time to inefficacy of 10 months, IQR 5.84-17.64). Gastrointestinal intolerance was the main reported toxicity (46.15%). In univariate analysis, anti-citrusulinated protein antibodies (ACPA) positivity, alcohol consumption, lack of comorbidities, hepatic toxicity, higher 6_DAS28, swollen joint count and tender joint count on the 6th month of therapy were associated to lower retention rates. In multivariate analysis, lack of comorbidities (HR=3.3, CI 95% 1.4-7.8, p=.006) and higher 6_DAS28 (HR=0.32, CI 95% 0.14-0.72, p=.006) were independent predictors of suspension of combination therapy. Moreover, both male gender (HR=2.87, 95% CI 1.2-6.56, p=.016) and positivity to ACPA (HR=0.1, 95% CI 0.01-0.73, p=.024) were independent predictors of toxicity. There was also higher tendency to toxicity, but without statistical significance, in alcohol consumers (p=.08). Regarding inefficacy, smoking habits (HR=0.15, 95% CI 0.04-0.52) and 3>DAS28 (HR=0.15, 95% CI 0.04-0.53) were independent predictors.

Conclusion: Addition of LFN to MTX showed an early positive response. However, it was frequently associated to toxicity, and less than half of the patients continued with this therapeutic strategy after 5 years of follow up. Male gender, smoking habits and positivity to ACPA were predictors of worse outcome, as already reported in literature [1]. Lack of comorbidities was an independent predictor of suspension. This can be explained by the fact that physicians tend to adopt a more aggressive strategy on patients without comorbidities, switching earlier to bDMARDs/tDMARDs.

This study also showed that early response to combination therapy is an independent predictor on drug retention, suggesting that decisions on treatment strategy should be made early after the beginning of MTX/LFN.

References:

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