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AB0192

RHEUMATOID ARTHRITIS: IS IT WORTH IT TO ADD LEFLUNOMIDE TO METHOTREXATE IN REFRACTORY DISEASE?

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Background: In refractory rheumatoid arthritis (RA), adding other classic synthetic disease-modifying antirheumatic drug (csDMARD) such as leflunomide (LFN) to methotrexate (MTX) is one suitable option [1,2]. Yet, there are safety issues to consider which may limit this strategy, but also regarding its true effectiveness in avoiding exposure to biological DMARDs (bDMARD) or target synthetic DMARDs (tsDMARD).

Objectives: 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. Sociodemographic information, comorbidities, disease related information, adverse reactions and disease activity according to Disease Activity Score 28

– C reactive protein (DAS28) were recorded at baseline and after 3, 6 and 12 months of combination therapy (3_DAS28; 6_DAS28; 12_DAS28, respectively). Information regarding toxicity (need to dose adjustment/suspension) and inefficacy (add/switch to bDMARD/tsDMARD) were recorded. Follow-up was considered until last medical record available. SPSS was used for statistical analysis. Kaplan Meier and Cox-regression were used for univariate and multivariate analysis, respectively, significant level was 2-sided $p < .05$.

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 (4.01 ± 1.01 to 2.57 ± 1.52 , $p = .003$; Δ DAS28 = 1.58 ± 1.17). However, during a median follow up time of 64 (IQR 39-83) months, 58.44% of patients needed to change treatment strategy, 66.67% 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-citrullinated 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 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/tsDMARDs.

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.

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AB0193

ROLE OF DICKKOPF-1 IN RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is characterized by persistent synovitis that leads to structural joint damage causing deformity and disability. 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 is a secreted glycoprotein that also acts as a potent negative regulator of wntless signaling. Current therapies used to treat RA are not able to effectively repair damaged bone. There is a strong relationship between Wnt signaling pathway, RA and DKK-1 so; this relationship may be a therapeutic point of interest

Objectives: To assess the correlation between Dickkopf-1 and RA disease activity, disability, severity and functional status.

Methods: Fifty patients fulfilled the 2010 ACR -EULAR criteria for RA were included. Twenty five healthy age and sex matched individuals served as a control (for assessment of serum DKK-1 level). Excluded from the study, patients with Paget disease, Multiple myeloma, Breast cancer, Bone metastasis, Diabetes mellitus, Hyperthyroidism, patients on medication that influence bone metabolism as: heparin, anticonvulsant or thyroxine.

All patients were subjected to full history and examination. Disease activity measures as disease activity score (DAS 28-ESR), Visual analogue scale (VAS) and Disease disability indices including ACR criteria of functional status in RA and Health assessment questionnaire disability index (HAQ-DI). Erythrocyte sedimentation rate (ESR), C-Reactive protein (CRP), Rheumatoid factor (RF), Anti citrullinated peptide antibody (ACPA) and Serum dickkopf-1 level. Simple erosion narrowing score (SENS) and Ultrasound DAS (US DAS) were done

for all patients. Ultrasound DAS included 28 joints, Power Doppler ultrasound (PDUS) examination of 22 joints and gray scale ultrasound (GSUS) examination for Effusion/Hypertrophy (E/H) of 28 joints. Ultrasound erosion count (USEC) and Ultrasound erosion rate (USER) were assessed.

Results: Dickkopf-1 level in RA patients ranged from 66 to 453 ng/ml while in the control group ranged from 15 to 87 ng/ml with statistically significant difference. RA patients were grouped in to: group 1 included 15 (30%) patients with normal DKK-1 level and group 2: included 35 (70%) patients with elevated DKK-1. The differences between both groups were highly significant regarding clinical and laboratory measures (duration of morning stiffness, DAS 28, VAS, ESR, CRP, RF and ACPA), and regarding HAQ-DI, SENS and US DAS. We found significant positive correlation between DKK-1 level and laboratory measures (ESR, CRP, RF, ACPA), radiographic parameters (SENS and erosion score), ultrasonographic parameters (US DAS, USEC and USER) and with HAQ-DI and functional status.

Conclusion: Serum level of dickkopf-1 was elevated in RA patients and the results demonstrated the relationship between increased dickkopf-1 level and increased disease activity, decreased functional capacity and chronic structural damage suggesting its important role in the pathogenesis of RA.

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AB0194

VITAMIN D TRAJECTORIES IN EARLY DIAGNOSED, AGGRESSIVELY TREATED RHEUMATOID ARTHRITIS PATIENTS: A 10 YEAR LONGITUDINAL COHORT STUDY BASED ON THE DANISH CIMESTRA TRIAL

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Background: Low vitamin D levels are common in Rheumatoid Arthritis (RA)¹, and possibly associated with disease course,² but data on vitamin D levels during long-term disease course has not been reported previously.

Objectives: To describe vitamin D trajectories from time of diagnosis through 10 years follow-up in early diagnosed RA patients.

Methods: The CIMESTRA trial included 160 newly diagnosed RA-patients, treated aiming at remission with methotrexate and intraarticular steroid, further randomized to ciclosporine or placebo. Vitamin D supplementation was recommended according to national guidelines. Vitamin D_{total} was measured at diagnosis, and year 1, 5 and 10 using LC-MS/MS. 1,25(OH)₂D was measured at diagnosis and year 1 using RIA. Linear mixed effects models were used to study vitamin D levels serially. We had fixed effects for time, and patients modelled as a random effect. We tested the hypothesis that percentage of patients achieving D_{total} ≥ 50 nmol/l during follow-up was 90%. Analyses of associations between D_{total} and DAS28-CRP during the disease-course were adjusted for age, sex, symptom-duration prior to diagnosis and season of diagnosis.

Results: Median D_{total} at baseline was 53 nmol/l (IQR 36-567.8). D_{total} increased significantly during follow-up, independently of level at diagnosis (p<0.001). Individuals achieving D_{total} ≥ 50 nmol/l during follow-up was 80-87%, but not as high as 90% at year 1 and 5, p<0.002. DAS28-CRP during disease-course was inversely associated with D_{total} trajectories only in crude (β-coefficient (β) -0.0034, 95%CI (-0.007; -0.0002) p=0.039) and partially adjusted analyses (β -0.003, 95%CI (-0.007; -0.002) p=0.04). Estimate was left insignificant in fully adjusted analyses (β -0.003, 95%CI (-0.0006; 0.0001) p=0.06). 1,25(OH)₂D levels did not change significantly during follow-up (p=1.00).

Conclusion: D_{total} increased significantly during follow-up, but fewer than 90% achieved the recommended 50 nmol/l at year 1 and 5. Disease activity during follow-up was associated with D_{total} trajectories only in partially adjusted analyses, while adjustment for possible confounders left estimates insignificant. Results suggest vitamin D supplementation to be recommended in all RA patients.

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