Background: In refractory rheumatoid arthritis (RA), adding other classic synthetic disease-modifying antirheumatic drugs (csDMARDs) such as leflunomide to MTX may be an effective strategy in avoiding exposure to biological DMARDs (bDMARD) or target synovitis therapies to consider which may limit this strategy, but also regarding its true effectiveness in avoiding exposure to biological DMARDs (bDMARD) or target synovitis.

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

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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) is a secreted protein that is strongly associated with subchondral bone erosion in RA; Dkk-1 is a secreted glycoprotein that also acts as a potent negative regulator of wingless signaling. Current therapies used to treat RA are not able to effectively repair damaged bone. Dkk-1 is a strong regulator 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, Diabes mellitus, Hyperthyroidism, patients on medication that influence bone metabolism as: heparin, anticonvulsant or thyroxin.

Disclosure of Interests: None declared

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- 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/sub 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<0.05.

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 (p=0.01 to 2.57±1.92, p<0.003; δDAS28 = 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, hepatitis B positiveness, and 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 positivity to ACPA (HR=2.87 , 95% CI 1.2-6.56, p=.016) were independent predictors of toxicity.

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 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.

References:

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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 into: group 1 included 15 (30%) patients with normal DKK1 level and group 2: included 35 (70%) patients with elevated DKK1. The differences between both groups were highly significant regarding clinical and laboratory measures (duration of morning stiffness, DAS 28, VAS, ESPR, RF and ACPA), and regarding HAQ-DI, SENS and US DAS. We found significant positive correlation between DKK1 level and laboratory measures (ESPR, 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.

**References:**


**Disclosure of Interests:** None declared.

**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), and possibly associated with disease course, 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 treated aiming at remission with methotrexate and intraarticular steroid, further treated aiming at remission with methotrexate and intraarticular steroid, further treated aiming at remission with methotrexate and intraarticular steroid, further treated aiming at remission with methotrexate and intraarticular steroid, further treated aiming at remission with methotrexate and intraarticular steroid, further treated aiming at remission with methotrexate and intraarticular steroid, further treated aiming at remission with methotrexate and intraarticular steroid, further treated aiming at remission with methotrexate and intraarticular steroid, further treated aiming at remission with methotrexate and intraarticular steroid, further treated aiming at remission with methotrexate and intraarticular steroid, further treated aiming at remission with methotrexate and intraarticular steroid, further treated aiming at remission with methotrexate and intraarticular steroid, further treated aiming at remission with methotrexate and intraarticular steroid, further treated aiming at remission with methotrexate and intraarticular steroid.

**Results:** Dtotal 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 Dtotal 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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