of insufficient efficacy. Difficult-to-treat (D2T) RA is defined as refractory to two or more b/ts DMARDs with different mechanisms of action, with active and progressive disease, as published by Eular(3)

Objectives: To evaluate real world efficacy of approved JAKis switching in patients with D2T RA who were unable to control their disease activity due to insufficient efficacy despite the sequential use of multiple bDMARDs and JAKis, focusing on the drug retention rate.

Methods: In our hospital, RA was diagnosed according to the 1987 or 2010 classification criteria, and when two or more bDMARDs (including both TNFis and non-TNFis) were inadequately effective, it was defined as D2T RA. We retrospectively investigated patients who switched to JAKis for D2T RA. The drug retention rate was investigated by the Kaplan-Meier method, and the difference was tested by the Logrank test.

Results: The 1-year retention rate of JAKis for D2T RA was 50.8% in TOF 38 cases [28 women, age average 70.2 years, disease duration average 12.4 years, past bDMARDs use average 3.5 drugs, MTX combination 9 cases, DAS28 ESR average 4.11] and 66.3% in BAR 35 cases [26 cases, 73.0 years old, 14.8 years, 4.17 agents, 9 cases, 3.68], and there was no significant difference ($P = 0.30$). Among them, there were 17 cases [11 cases, 70.6 years old, 13.5 years, 4.18 drugs, 2 cases, 3.65] of switching between JAKis, all of which were switching from TOF to BAR. The 1-year retention rate was 45.8% [reason for discontinuation: insufficient effect in 3 cases, adverse events in 6 cases], which was not significantly different but tended to be lower than 72.7% [reason for discontinuation: insufficient effect in 1 case, adverse event in 2 cases, patient's convenience in 1 case] in 16 patients [13 cases, 76.3 years old, 17.1 years, 3.19 drugs, 7 cases, 3.69] who received BAR as the first JAKi for D2T RA patients ($P = 0.089$).

Conclusion: Although the number of cases is small in the retrospective survey, it is suggested that the retention rate of BAR switched to D2T RA may be slightly lower in patients with a history of TOF discontinuation due to insufficient efficacy than in JAKi naive patients. It is expected that the number of new JAKi usage cases will increase in the future, and it is necessary to consider switching between other JAKis in addition to switching from BAR to TOF.

REFERENCES:

- [1] Smolen JS, Landewe R, Bijlsma J et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis* 2017;76:960-77.
- [2] Rendas-Baum R, Wallenstein GV, Koncz T et al. Evaluating the efficacy of sequential biologic therapies for rheumatoid arthritis patients with an inadequate response to tumor necrosis factor- α inhibitors. *Arthritis Res Ther* 2011;13:R25.
- [3] Nagy G, et al. EULAR definition of difficult-to-treat rheumatoid arthritis. *Ann Rheum Dis* 2021;80:31-35. doi:10.1136/annrheumdis-2020-217344.

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AB0253

COMPARISON OF PHARMACODYNAMICS OF METHOTREXATE AS METHOTREXATE-POLYGLUTAMATES CONCENTRATIONS IN RHEUMATOID ARTHRITIS; INTERIM DATA EVALUATION OF MIRACLE STUDY CONDUCTED IN JAPAN, KOREA AND TAIWAN

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Background: Methotrexate (MTX) is the first-line therapy for rheumatoid arthritis (RA). The concentrations of MTX-polyglutamates (PG) in erythrocytes, an active form of MTX, are useful markers for the optimal usage of MTX in patients with RA. The concentrations of MTX-PG have been reported to be different between Japanese and Caucasians. However, the difference among Asian ethnicity remains unclear.

Objectives: To examine MTX-PG concentrations in association with MTX dose during the first 24 weeks after the initiation of MTX for newly diagnosed RA patients in Japan, Korea and Taiwan.

Methods: MIRACLE study is a multicenter, open-label, randomized, 48 weeks interventional study conducted in Japan, Korea and Taiwan to evaluate non-inferiority of low dose to high dose of MTX as an add-on therapy to adalimumab in 300 patients with RA who do not achieve remission after 24 weeks MTX monotherapy in stipulated dosage. In the first 24 weeks, MTX was started at 6 to 8 mg/week for newly diagnosed RA patients, and promptly escalated to the maximum tolerable dose in 12 weeks in principle. This interim data evaluation was intended to investigate the differences among countries in the relationship between MTX dose, safety and MTX-PG concentrations in erythrocytes during the first 24 weeks. The efficacy of the treatment is not included at this point.

Results: A total of 166 patients (106 in Japan, 35 in Korea, 25 in Taiwan) were included in this interim data. The age at treatment initiation was 57.2 years old on average and female was 79.5%. The time course changes in total and individual MTX-PG levels differed in the three countries. At 24 weeks, whereas the mean total MTX-PG concentrations were comparable (112.9 nmol/L in Japan, 104.4 nmol/L in Korea, and 115.7 nmol/L in Taiwan) with a dose of MTX of 12.3mg/week, 14.1mg/week, and 12.2mg/week, respectively, the individual MTX-PG concentrations were different. The MTX-PG1 and MTX-PG2 concentrations were lower in Korea than Japan and Taiwan whereas MTX-PG3, MTX-PG4 and MTX-PG5 concentrations were the highest in Korea.

Conclusion: The distribution of short-chain and long-chain MTX-PG concentrations were various among Asian countries despite similar dose of MTX administration: NCT03505008.

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AB0254

NEUROPSYCHIATRIC ADVERSE DRUG REACTIONS ASSOCIATED WITH LOW DOSE METHOTREXATE IN RHEUMATOID ARTHRITIS PATIENTS

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Background: Neuropsychiatric adverse drug reactions (NPADRs) are well known with high dose methotrexate treatment. However, NPADRs have also been observed with low dose methotrexate (LDMTX) treatment in real world rheumatology data.

Objectives: To evaluate the association between LDMTX and NPADRs, the impact of these NPADRs on further treatment and on health related quality of life (HRQoL) in patients with rheumatoid arthritis (RA) using real world data.

Methods: The nature and frequency of NPADRs associated with LDMTX in the Dutch DREAM-RA registry were described. We assessed the causality of each NPADR with the Naranjo Probability Scale (NPS), the impact of NPADRs on further LDMTX treatment and the impact on patient reported HRQoL. NPADRs were structured using terminology of the Medical Dictionary for Regulatory Activities.

Results: A total of 71 NPADRs (frequency 6.8%) associated with LDMTX were captured in the DREAM-RA registry. NPADRs were registered for 62 (5.9%) out of 1048 patients with 10.9 NPADRs per 1000 patient years (Table 1). The most frequently reported NPADRs were headache, dizziness and depression. The causality was considered probable for 67 NPADRs (94.4%) and definite for 1 NPADR (1.4%). The NPADRs led to LDMTX withdrawal in 34 cases (47.9%) and LDMTX was not restarted in 16 cases (47.1%). Median mental HRQoL was significantly decreased around the occurrence of the NPADR and remained significantly lower after the event. Median physical HRQoL was not significantly affected.

Table 1. Baseline characteristics of DREAM-RA patients using methotrexate with at least one neuropsychiatric adverse drug reaction

Characteristics N=62	N (%)
Female sex	40 (64.5%)
Age in years, mean (± SD), range	59.8 (± 13.1), 25 – 82
Rheumatoid factor	Positive 43 (69.4%) Negative 13 (21.0%) Unknown 6 (9.7%)
Anti-CCP, n (%)	Positive 34 (54.8%) Negative 19 (30.7%) Unknown 9 (14.5%)
Methotrexate dosage in mg/week, mean (± SD)	18.7 (± 5.9)
Specific methotrexate dosage	< 15 mg / week 5 (7.0%) 15 mg/week 28 (39.4%) 20 mg/week 11 (15.5%) 25 mg/week 14 (19.7%) 30 mg/week 5 (7.0%) Unknown 8 (11.3%)
Concomitant medication at moment of NPADR	Folic acid 68 (95.8%) Prednisolone 20 (28.2%)

Anti-CCP: anti cyclic citrullinated peptides, NPADR: neuropsychiatric adverse drug reaction, SD: Standard Deviation

Conclusion: The association between NPADRs and LDMTX in RA patients was recognised by HCPs and frequently led to LDMTX withdrawal and a decrease in mental HRQoL. Many NPADRs scored 'probable' using the NPS. Knowledge on the nature, frequency and impact of these NPADRs will enhance attention towards potential NPADRs during LDMTX therapy allowing better risk assessment and communication to patients.

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AB0255

BASELINE CHARACTERISTICS OF PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH UPADACITINIB IN GERMAN REAL-WORLD PRACTICE: RESULTS FROM THE POST-MARKETING OBSERVATIONAL UPwARds STUDY

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Background: The efficacy and safety of upadacitinib (UPA), a selective Janus kinase inhibitor, has been evaluated in the SELECT rheumatoid arthritis (RA) clinical program,¹⁻⁶ but its real-world effectiveness remains to be investigated. The UPwArds study will assess the association of C-reactive protein (CRP) level with remission and other efficacy outcomes in patients with RA treated with UPA in German real-world practice.

Objectives: To describe the baseline characteristics of patients enrolled in the UPwArds study.

Methods: The prospective, open-label, multicenter, non-interventional, post-marketing UPwArds study included adult patients with moderate-to-severe RA (swollen joint count [SJC28] ≥3 and inadequate response or intolerance to ≥1 disease-modifying antirheumatic drug [DMARD]). Patients were treated with UPA 15 mg once daily, as monotherapy or in combination with methotrexate (MTX; 50:50 mono:combo enrollment planned), according to the German label. Variables assessed included medical history (disease duration, previous RA therapy, and vaccination status), CRP level, and disease activity (disease activity score [DAS28(CRP)], tender joint count [TJC28], and SJC28). There was no recruitment restriction regarding CRP level. This descriptive interim analysis reports patient baseline characteristics after enrollment was complete. All data were analyzed as observed, with no imputation of missing data.

Results: 533 patients (UPA monotherapy: 257 [48%]; UPA plus MTX: 276 [52%]) were included. Mean patient age was 58 years; mean disease duration was 9 years (Table 1). Despite having active RA, almost half the population (44%; n=237) did not have elevated CRP at the start of UPA treatment. Mean DAS28(CRP) was 4.6; mean TJC28 and SJC28 were 7.7 and 5.6, respectively. Overall, 39% of patients had not been treated with any biologic (b) DMARD or targeted synthetic (ts) DMARD before enrollment; 25% and 36% had previously been treated with 1 or ≥2 bDMARDs or tsDMARDs, respectively (Figure 1). 8.7% of patients had previously received a herpes zoster vaccination (8.1% Shingrix; 0.6% Zostavax).

Conclusion: In German clinical practice, the population of patients with RA in the UPwArds study was predominantly treatment-refractory. Half of these patients had no elevated CRP despite active disease; future analyses will assess the impact of CRP on efficacy outcomes.

REFERENCES:

- [1] Smolen JS, et al. Lancet 2019;393:2303–11;
- [2] Burmester GR, et al. Lancet 2018;391:2503–12;
- [3] Genovese MC, et al. Lancet 2018;391:2513–24;
- [4] van Vollenhoven R, et al. Arthritis Rheumatol 2020;72:1607–20;
- [5] Fleischmann R, et al. Arthritis Rheumatol 2019;71:1788–800;
- [6] Rubbert-Roth A, et al. N Engl J Med 2020;383:1511–21.