patients, was used to determine methotrexate (MTX) intolerance prevalence in RA patients. The MISS consisted of four domains: abdominal pain, nausea, vomiting, and behavioral symptoms, occurring before (anticipatory), after, and when thinking of MTX (associative). MTX intolerance was defined as six or more points on the MISS. Our statistical analysis was based on a descriptive study and logistic regression with SPSS20.

Results: We included 102 RA patients with a mean age of 51.60 ± 14.33 years. Women were predominant (93.1%). The mean disease duration was 14.86 ± 9.78 years, with a mean methotrexate use duration of 7.42 ± 6.44 years. The mean dose of methotrexate was 12.13 ± 9.06 mg per week. The prevalence of methotrexate intolerance was 55.9%, and seventy-six patients (74.5 %) experienced at least one gastrointestinal symptom during MTX treatment. After MTX administration, the most prevalent gastrointestinal symptom was nausea (93% of the intolerant patient), whereas abdominal pain occurred in 73.7% and vomiting in 57.9%. These symptoms were also prevalent before and when thinking of MTX. Anticipatory nausea was reported in 45.6% and associative nausea in 54.5% of the cases, abdominal pain occurred anticipatory in 22.8% and associative in 42.1 %, anticipatory vomiting was the least prevalent, affecting 8.8 %. Behavioral symptoms affected 87.7% of intolerant patients, with restlessness being the most prominent symptom in 71.9% of them. Among the intolerant patients, 45 patients (79%) took parenteral MTX, and 12 (21.1%) took methotrexate orally. In comparison, young patients (49.11 ± 14.95 years) were more intolerant to MTX than old (54.76 ± 13 years, $p = 0.048$) ones. However, in univariate logistic regression analysis, we did not find any significant association between methotrexate administration route, dose, duration, and digestive intolerance.

Conclusion: Methotrexate intolerance was highly prevalent in our RA population. These results strengthen the idea that early detection of MTX intolerance may avoid effective treatment discontinuation, especially in younger patients.

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AB0275

TOFACITINIB EFFECTIVENESS IN PATIENTS WITH RHEUMATOID ARTHRITIS AFTER CONVENTIONAL OR BIOLOGICAL THERAPY - IT REAL ROLE IN DIFFERENT LINES OF TREATMENT

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Background: rheumatoid arthritis (RA) is a chronic and disabling autoimmune disease, with a high clinical and economic burden. This implies the need to investigate therapies that maximize clinical results. Tofacitinib is recommended as a different alternative to biologic therapy when a patient remains with moderate or high disease activity after conventional DMARDs use, or as an option after failure to biologic therapy.

Objectives: to evaluate the effectiveness of Tofacitinib in RA as first-line (after conventional DMARDs failure) or second-line treatment (after biologic therapy failure) in a real-life cohort of RA patients and its differences.

Methods: this is a descriptive retrospective cohort study conducted at a specialized center for RA in Bogota, Colombia; databases from 2017 to 2019 were used to select and study patients with indication of Tofacitinib, regardless of their previous treatment or disease status. The indication and initiation of Tofacitinib (5mg BID or 11 mg once daily) was an independent medical decision made as part of the individualized management of every patient. Effectiveness was evaluated in those patients who met the high adherence criteria (at least three visits with a rheumatologist per year), with no change or addition of other conventional DMARDs. Frequencies and proportions in baseline characteristics, differences in disease activity were calculated between the first and second line tofacitinib treatment. Comparisons of continuous variables data between the two patient groups were made using the t-test; the chi-square test and Fisher's exact test were used for statistical analysis of categorical variables. Logistic regressions were performed to analyze related factors with therapeutic response outcomes.

Results: we included 152 RA patients who received tofacitinib: first-line (T1) (n= 85, 55.9%) or second-line (T2) (n= 67, 44.1%). T1 first-line group was younger than the T2 second-line patients (53 ± 12.8 years and 59 ± 11.4 years, p -value 0.01) and they had a shorter disease duration than T2 patients (11.8 vs. 12.8 years, p -value 0.01). Comparative analysis of response to treatment showed a reduction in DAS28 at 3, 6 and 12 months in both study groups. The response in disease activity at 3 months was a major factor related to 6-month response (OR 13.4,

95% CI 4.5-39.4, p value 0.000), while non-response at 3 months were associated with no response at 6 months of follow-up. Baseline DAS28 was significantly associated with response at 12 months (OR 1.9, 95% CI 1.11-3.25, p -value 0.028). At 12 months of treatment, both groups showed disease response and control according to the DAS28 from baseline, but a higher proportion of T1 patients achieved remission (45% vs 23%). A subgroup analysis to evaluate T2 second-line Tofacitinib therapy showed no statistically significant differences in any response criteria according to the number of previously received biologicals.

Table 1. Regression analysis (risk of response of the disease at 6 and 12 months of treatment with Tofacitinib)

Factor	Response at Month 6			Response at Month 12*		
	OR	IC95%	P value	OR	IC95%	P value
Age	1.00	0.97-1.03	0.788	1.02	0.98-1.06	0.211
Male	1.82	0.65-5.08	0.251	0.81	0.27-2.38	0.709
Duration of RA	0.99	0.94-1.04	0.908	1.02	0.96-1.08	0.444
Positive Rheumatoid Factor	0.81	0.26-2.56	0.730	0.63	0.17-2.26	0.485
Positive Anti-CCP	0.34	0.068-1.6	0.189			
Initial DAS28	1.61	1.04-2.49	0.033	1.9	1.11-3.25	0.018
First line	0.44	0.19-1.01	0.054	1.47	0.56-3.83	0.423
Treatment period	1.12	0.80-1.55	0.492	1.1	0.75-1.61	0.607
Dose: 11 mg.	0.95	0.42-2.13	0.904	0.75	0.258-1.9	0.565
Response at Month 3	13.42	4.57-39.4	0.000	2.32	0.87-6.18	0.091

*Positive Anti-CCP at month 12 was omitted because of collinearity

Conclusion: Tofacitinib is an effective treatment option for patients with RA after conventional DMARDs and in patients after biologic therapy failure, but maybe is better used it as a T1 first-line of treatment. Further studies are required to determine the real role of tofacitinib in different lines of RA treatment.

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AB0276

HOW FAST CAN METHOTREXATE BE ESCALATED IN RHEUMATOID ARTHRITIS? A MULTICENTRE, PARALLEL-GROUP RANDOMIZED CONTROLLED TRIAL (MEIRA)

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Background: Literature regarding the optimal dose escalation strategy of methotrexate (MTX) in RA is scant and ambiguous (1). Concerns regarding the safety of rapid escalation may lead to delayed attainment of the optimal dose and treatment target.

Objectives: To compare the efficacy, safety and tolerability of fast versus usual dose escalation of oral MTX in RA.

Methods: This multicenter, open-label (assessor blinded) RCT included patients with active RA (SJC $\geq$ 2 and TJC $\geq$ 4) aged 18-55 years, not on DMARDs (except HCQ and/or low-dose prednisolone) and with disease duration <5 years. Patients were randomized 1:1 into two groups with the same starting dose of oral MTX (15mg/week), but escalated either by 5mg every 2 weeks (fast escalation group) or 5mg every 4 weeks (usual escalation group), till a maximum of 25mg/wk. Primary outcome was proportion of EULAR good responders at 16 weeks. Secondary outcomes were change in DAS28-3 and EULAR responders (good or moderate) at 8 and 16 weeks, change in Indian HAQ at 16 weeks, and symptomatic (questionnaire based) and laboratory adverse effects over 16 weeks. RBC MTX polyglutamate-3 levels were measured using HPLC in both groups. There was an open-label extension phase till 24 weeks (use of other DMARDs was permitted beyond 16 weeks if target was not met), and DAS28-3 at 24 weeks was compared.

Trial Reg: CTRI/2018/12/016549

Results: 178 patients (mean age 39.8 (8.6) years, 84% females) with mean disease duration of 1.9 (1.4) years were randomized (89 in each group). Mean DAS28ESR-3 and DAS28CRP-3 at enrollment were 6.3 (0.9) and 5.4 (1.1). At 16 weeks, there was no significant difference in good EULAR response by DAS28ESR-3 (5.6, 7.9%, $p=0.9$) or DAS28CRP-3 (28.1, 22.5%, $p=0.8$) between the two groups (Figure 1).

The change in DAS28-ESR-3 at 8, 16 and 24 weeks (or by DASCRP-3, not shown) and improvement in HAQ at 16 weeks were also not significantly different (Table 1). Notably, there was no significant difference in symptomatic GI or CNS adverse effects, incidence of cytopenia, transaminitis or rates of drug discontinuation. RBC MTX polyglutamate-3 levels at 8 and 16 weeks were also similar (Table 1).

Figure 1. EULAR response and change in DAS28-ESR-3 over time

Table 1. Key secondary efficacy and safety outcomes

Parameter	Usual	Fast	p-value
Efficacy			
Delta DAS28-ESR-3 (Mean±SD)			
-8 wk			
-ITT (n=178)	-0.9 ± 1.0	-0.8 ± 0.9	0.5
-PP (n=139)	-1.2 ± 1.0	-1.1 ± 1.0	0.5
-16 wk			
-ITT	-1.3 ± 1.1	-1.3 ± 1.0	0.9
-PP	-1.6 ± 1.1	-1.6 ± 0.9	1
-24 wk			
-ITT	-1.6 ± 1.3	-1.5 ± 1.1	0.3
-PP	-2.1 ± 1.2	-1.8 ± 1.1	0.14
Delta Indian HAQ (16 wk)	-0.7 ± 0.6	-0.8 ± 0.6	0.2
Adverse effects			
Serious AE	0	0	-
Death	0	0	-
Symptomatic AE ever* n (%)			
Vomiting	7 (8)	7 (8)	1
Nausea	22 (26)	26 (30)	0.5
Stomach ache	16 (19)	17 (20)	0.9
Loss of appetite/bad taste	21 (25)	27 (31)	0.3
Lethargy	20 (24)	21 (25)	1
Dizziness	19 (23)	16 (19)	0.5
Irritability/anxiety	14 (16)	14 (16)	1
Laboratory AE ever* [n/N times done (%)]			
Transaminitis episodes (>40 IU/L)	52/224 (23)	52/219 (24)	0.9
-Significant (>80 IU/L)	5/224 (2)	8/219 (4)	0.4
Thrombocytopenia episodes (<150000/uL)	10/224 (5)	13/218 (6)	0.5
-Significant (<100000/uL)	2/224 (1)	2/218 (1)	1
Leucopenia episodes (<4000/uL)	2/224 (1)	3/220 (1.5)	0.8
-Significant (<3500/uL)	1/224 (0.5)	2/220 (1)	0.8
Methotrexate levels			
MTX-polyglutamate-3 (nmol/L)			
-8 wk	25.8 ± 10.5	26.9 ± 13.6	0.6
-16 wk	40.7 ± 20.9	40.1 ± 23.4	0.9

*Ever=any time during the study/ITT= intention-to-treat, PP=per-protocol, AE=adverse effect

Conclusion: A faster escalation of MTX (5 mg every 2 weeks) reaching 25 mg/week by 4 weeks did not have a significantly higher rate of adverse effects (symptomatic or laboratory) compared to an escalation by 5 mg every 4 weeks. Although not more efficacious, it may shorten the time to recognize MTX failure, and optimize treat-to-target.

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AB0277

ASSOCIATION BETWEEN INTRA-ERYTHROCYTE METHOTREXATE POLYGLUTAMATE CONCENTRATION AND CLINICAL RESPONSE IN RHEUMATOID ARTHRITIS IN PATIENTS TREATED WITH METHOTREXATE INJECTABLE SUBCUTANEOUSLY

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Background: Methotrexate (MTX) is the first-line treatment for rheumatoid arthritis (RA). Due to its short half-life, blood MTX dosage is not performed in current practice. Erythrocyte MTX-polyglutamate (MTX-PG), which penetrates into the red blood cells, would be correlated with the area under the MTX curve and would be more accessible for dosing. When treatment is initiated, its concentration correlates with efficacy and therapeutic adherence.

Objectives: To determine the interest of erythrocyte MTX-PG dosage in case of failure of 1st line MTX treatment.

Methods: In this single-centre cross-sectional study, RA patients presenting for consultation at the Saint-Etienne University Hospital, with a stable dose of MTX for more than 3 months at least 15 mg/week subcutaneously with either clinical remission (DAS28<2.6) or active disease (DAS28>3.2) were included between July 2nd 2018 and May 28th 2020. In order to assess therapeutic compliance, the patient completed the compliance questionnaire of Rheumatology (CQR) questionnaire. The determination of erythrocytic MTX-PG was performed on a 5 mL blood sample by liquid chromatography method for the determination of the different PG forms.

Results: Sixty patients were included, 34 in the active RA group and 26 in the RA group in remission. One patient withdrew his consent. Only 16% of patients were observed with a CQR score > 80%. Patients in remission were leaner with a longer duration of disease and MTX treatment. The sex ratio, RA status, creatinine clearance and MTX dose was not different in both groups. The CQR was better in the remission group than in the active RA group. However, total MTX-PG was not different in the two groups. The same results were observed for the different forms of MTX-PG 1, 2, 3 or 4. In contrast, in the remission PR group, total MTX-PG or MTX-PG2, 3, 4 and 5 correlated inversely with BMI while MTX-PG3 correlated positively with BMI in the active PR group. In the active PR group, MTX-PG5 correlated with MTX dose.

Conclusion: MTX-PG dosage is not a biomarker of good response to MTX in our study. However, compliance is a key factor to be considered in RA with active disease in adapting patient management.

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