

Effect of non-adherence of methotrexate in patients with rheumatoid arthritis

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Background/Aims: Although methotrexate (MTX) is the first-line drug for management of rheumatoid arthritis (RA), non-adherence to MTX is highly prevalent and under-recognized. Here, we investigated adherence to MTX and its impact on clinical outcomes during follow-up in patients with RA.

Methods: In total, 367 RA patients were included in this study, with patient visits conducted annually for 4 consecutive years. Adherence was defined by the proportion of days covered during the follow-up period. We divided the patients into two groups; patients who took $\geq 80\%$ of their prescribed MTX doses and those who did not. In a prospective cohort, the generalized estimating equations were used to identify longitudinal associations between drug adherence and clinical outcomes including disease activity, physical function, and quality of life.

Results: Of the 367 RA patients, 8.7% were found to have taken MTX $< 80\%$ during the period of follow up. After adjustment for confounders, non-adherence to MTX was significantly associated with higher DAS28-ESR during the follow-up period (coefficient $\beta = 0.989$, 95% CI: 0.603–1.375; $p < 0.001$). In addition, non-adherence to MTX was a significant predictor of RAPID3 (coefficient $\beta = 1.847$; 95% CI: 0.221–3.472; $p = 0.026$) and EQ-5D (coefficient $\beta = -0.051$; 95% CI: -0.090–0.012; $p = 0.010$) after adjustment for confounding factors.

Conclusions: Non-adherence to MTX was significantly associated with worse clinical outcomes, as evidenced by higher disease activity, poorer physical function, and lower health-related quality of life during a 4-year follow-up of RA patients.

Table. Univariable and multivariable regression analyses by GEE model of the DAS28-ESR associated based on MTX adherence.

Response: DAS28-ESR	Univariable analysis		Multivariable analysis	
	Beta (95% CIs)	p value	Beta (95% CIs)	P value
Non-adherence to MTX	0.979 (0.595–1.362)	<0.001	0.989 (0.603–1.375)	<0.001
Female	-0.314 (-0.542–0.087)	0.007	-0.284 (-0.477–0.090)	0.004
Age, years	-0.006 (-0.013–0.002)	0.129		
Disease duration, months	-0.000 (-0.001–0.001)	0.913		
Education, > 12 years	0.142 (-0.037–0.321)	0.119		
Income, > 5,000 USD/month	0.202 (0.020–0.383)	0.030	-0.032 (-0.185–0.122)	0.687
Exercise	0.090 (-0.090–0.270)	0.327		
Rheumatoid factor	0.001 (0.000–0.002)	0.182		
Anti-CCP	-0.000 (-0.001–0.001)	0.741		
Hydroxychloroquine	-0.001 (-0.193–0.190)	0.988		
Sulfasalazine	0.243 (-0.702–1.188)	0.614		
Leflunomide	0.179 (-0.007–0.365)	0.059		
Tacrolimus	-0.430 (-0.905–0.045)	0.076		
Biologics	-0.256 (-0.559–0.047)	0.098		
Prednisolone dose, mg/day	-0.055 (-0.091–0.020)	0.002	-0.044 (-0.073–0.015)	0.003
Hypertension	-0.144 (-0.335–0.047)	0.140		
Diabetes mellitus	-0.113 (-0.036–0.135)	0.372		
COPD	-0.516 (-0.900–0.132)	0.009	-0.239 (-0.552–0.074)	0.134
Gastric ulcer	-0.096 (-0.275–0.084)	0.296	-0.266 (-0.768–0.286)	0.299

GEE: generalized estimating equations; MTX: methotrexate; DAS: disease activity score; ESR: erythrocyte sedimentation rate; CI: confidence interval; anti-CCP: anti-cyclic citrullinated peptide antibody; COPD: chronic obstructive pulmonary disease.