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Effectiveness, Tolerability, and Safety of Subcutaneous Methotrexate in Early Rheumatoid Arthritis: A Retrospective Analysis of Real-World Data From the St. Gallen Cohort

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BACKGROUND

Methotrexate (MTX) has been the cornerstone of treatment for rheumatoid arthritis (RA) for more than 30 years and has the highest 5-year retention rate of all disease-modifying antirheumatic drugs (DMARDs) at approximately 50%.[1-3]

Several studies have examined the clinical benefit of switching from oral to subcutaneous (SC) MTX, however, fewer studies have examined the clinical efficacy and safety of SC MTX in MTX-naïve patients. In addition, the real-world use of SC MTX in MTX-naïve patients has not yet been explored.

Table 1. Demographics and Baseline Characteristics

	All (N=70)	MTX-only (n=37)	MTX-biol (n=33)
Gender, female/male	40/30	19/18	21/12
Age, mean ± SD, years	56.1 ± 11.6	57.9 ± 13.1	54.2 ± 9.4
Follow-up, mean ± SD, years	1.8 ± 1.6	1.4 ± 1.3	2.2 ± 1.8
Disease duration, mean ± SD, years	1.6 ± 2.4	1.5 ± 2.4	1.6 ± 2.4
DAS28 at inclusion, mean ± SD	4.8 ± 1.3	4.7 ± 1.3	4.9 ± 1.4
RF positive at inclusion, %	65.7	67.6	63.6
ACPAs positive at inclusion, %	38.6	45.9	30.3
ESR at inclusion, mean ± SD, mm/h	28.0 ± 30.4	31.2 ± 36.4	24.6 ± 22.1
CRP at inclusion, mean ± SD, mg/L	19.4 ± 29.2	20.5 ± 31.7	18.0 ± 26.5
Baseline MTX dose, mean ± SD, mg/wk	15.7 ± 2.5	15.9 ± 3.0	15.6 ± 2.0
Baseline steroid dose, mean ± SD, mg/d	20.7 ± 9.5	17.8 ± 9.4	22.7 ± 9.5

ACPAs = anti-citrullinated protein antibodies; CRP = C-reactive protein; DAS28 = Disease Activity Score including 28 joints; ESR = erythrocyte sedimentation rate; MTX = methotrexate; RF = rheumatoid factor; SD = standard deviation.

METHODS

- Longitudinal, prospective, retrospective chart review
- Therapeutic decisions were made at the discretion of the treating clinician

Table 2: Inclusion/Exclusion Criteria

Inclusion	Exclusion
– RA consistent with 2010 ACR/EULAR criteria[4] – SC MTX as the first DMARD	– Previous treatment with conventional or biologic DMARDs – Oral MTX administration as the first exposure to MTX – Aged <18 or >80 years at disease onset – Lack of follow-up
Primary end point	

Primary end point

- Longitudinal disease activity as measured by DAS28 (Disease Activity Score including 28 joints)

Secondary end points included

- Time to employment of the first biologic agent
- Cumulative MTX and corticosteroid doses
- Reasons for termination of SC MTX treatment

Statistical analysis methods

- Smoothed curves of the raw data were produced using loess smoothing
- Comparisons of end points: linear mixed models with random intercept and slope

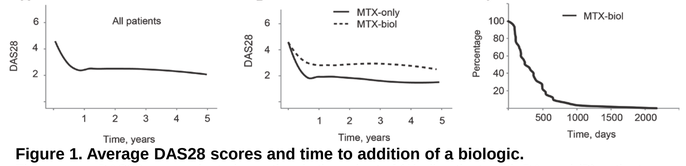

Figure 1. Average DAS28 scores and time to addition of a biologic.
The average DAS28 was evaluated over time in the cohort of (A) all patients with RA, and (B) patients with RA who did not require the addition of biologics (MTX-only, solid line) or those who required the addition of biologics (MTX-biol, dashed line). The time to addition of first biologic (C) for patients with RA who did require addition of biologics is also shown. DAS28, Disease Activity Score including 28 joints; MTX, methotrexate.

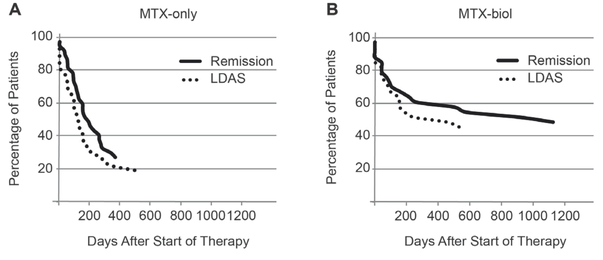

Figure 2. Time to LDAS and remission.
Time to LDAS (dotted line) and remission (solid line) for (A) patients with RA who did not require the addition of biologics (MTX-only) and (B) those who required the addition of biologics (MTX-biol). LDAS, low disease activity state; MTX, methotrexate.

OBJECTIVE:

- To assess the efficacy, tolerability, and safety of SC MTX in MTX-naïve patients with RA under real-world clinical circumstances

Table 5. Summary

	All	MTX-only	MTX-biol
Number of patients	70	37	33
DAS28 at 24 months	2.51	1.84	2.89
Time to therapeutic escalation (days)	n.a.	n.a.	387
Patients in LDAS (%)	80%	81.1	78.8
Time to LDAS	151.9	111.9	198.0
Patients in DAS remission	72.9	75.7	69.7
Time to DAS remission	213.7	145.7	297.1
Mean weekly MTX dose (mg)	18.2	17.4	19.1
Mean daily prednisone dose (mg)	6.0	5.4	6.7

DAS28 = Disease Activity Score including 28 joints; LDAS = low disease activity; MTX = methotrexate.

SAFETY:

- Mast frequent adverse events leading to cessation of MTX were gastrointestinal discomfort and lack of efficacy
- Seven severe infections were observed (**Table 4**)
- From the time to starting SC MTX through follow-up, 14 patients in the MTX-only group and 13 in the MTX-biol group required hospitalization

CONCLUSIONS:

- This study supports SC MTX as an effective and well-tolerated treatment option for patients with early RA in a real-world setting

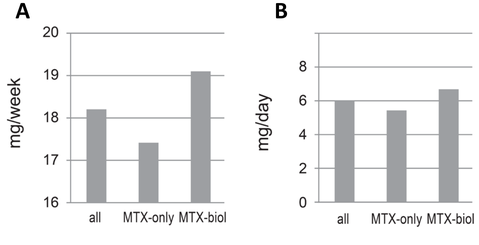

Figure 3. Average weekly doses of SC MTX and daily doses of prednisolone.
Average weekly doses of (A) SC MTX, and average daily doses of (B) prednisolone, for all patients, patients treated with only SC MTX (MTX-only), and patients requiring the addition of biologic agents (MTX-biol). MTX-only vs MTX-biol (Student's T-Test, P=0.09). MTX, methotrexate; SC, subcutaneous.

Table 3. Reasons for Stopping SC MTX

	All (N=70) n (%)
Discontinuation of SC MTX	32 (45.7)
Nausea/GI discomfort	7 (10.0)
Lack of efficacy	7 (10.0)
Remission	3 (4.3)
Patient decision	3 (4.3)
Interstitial lung disease	1 (1.4)
Cough	1 (1.4)
Allergic reaction	1 (1.4)
Aphthosis	1 (1.4)
Hair loss	1 (1.4)
Increase of liver enzymes	1 (1.4)
Infection	1 (1.4)
Progression of rheumatoid nodules	1 (1.4)
Renal failure	1 (1.4)
Resentment to injections	1 (1.4)
Start biologic monotherapy	1 (1.4)
Switch to oral MTX	1 (1.4)

GI = gastrointestinal; MTX = methotrexate; SC = subcutaneous.

Table 4. Serious Adverse Events

	MTX-only (n=37)	MTX-biol (n=33)
Severe infection, n		
Septic cholangitis + surgical revision	1	0
Urosepsis	1	0
Erysipelas	1	0
Soft tissue infection	0	1
Pneumonia	0	3
Other reasons for hospitalization		
Benign prostatic hypertrophy	2*	0
Ischiatica	1	0
Suspected osteomyelitis	1	0
Cataract	4†	1
Elective operative surgery of the knee	1	2
Facet joint infiltration	1	0
Arthrodesis	1	0
Ruptured aneurism	1	0
Bronchial carcinoma	1	0
Parkinson's syndrome	4‡	0
Active arthritis	0	8
Renal failure	0	1
Spinal stenosis	0	1
Lumbalgia	0	1
Incontinence	0	2§
Carpal tunnel syndrome	0	1
Coronary heart disease	0	3
Hospitalization for pulmonary symptoms	0	1

MTX = methotrexate.
*2 Events in the same patient.
†In 2 patients with 2 episodes each.
‡In 1 patient.
§In 1 patient.

References

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Disclosures

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