膠原病 Journal Club　　2022/11/8 住友

Efficacy and tolerability of subcutaneously administered methotrexate including dose escalation in long-term treatment of rheumatoid arthritis in a Japanese population

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[Mod Rheumatol. 2022 Sep 2;roac103.]

背景

- MTX poでは, 用量依存性に消化器副作用がみられる [Adv Clin Exp Med. 2019;28:1229-35.]. 日本では半数以上がMTX po 16mg/wに耐えられないと推定されている (JCR MTXガイドライン 2019).
- MTX poとMTX scの直接比較では, MTX sc のより高い bioavailabilityと, 優れた忍容性が示されている.
- 日本人を対象とした本論文を基に, 2022年9月MTX sc 製剤(メトジェクト®) が本邦で製造販売承認された.

[日本メディック　ホームページより]

2008 RCT MTX sc/po

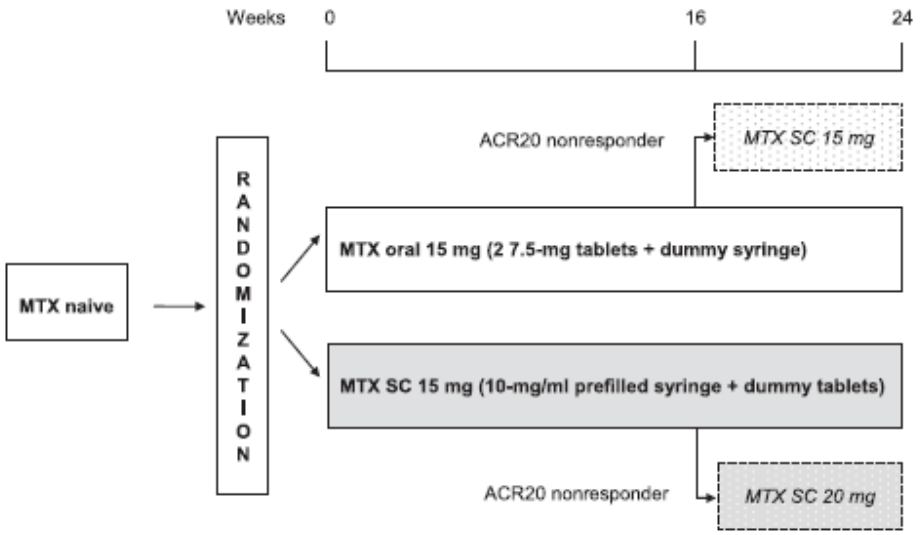
Comparison of the Clinical Efficacy and Safety of Subcutaneous Versus Oral Administration of Methotrexate in Patients With Active Rheumatoid Arthritis

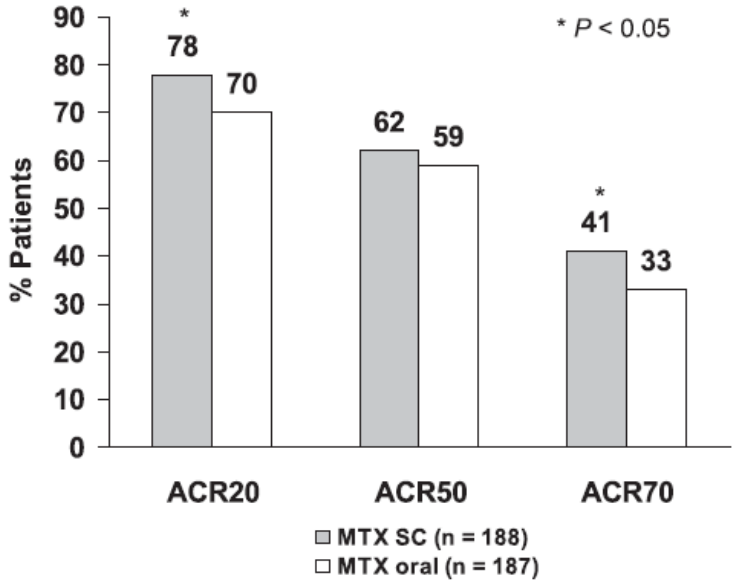
Results of a Six-Month, Multicenter, Randomized, Double-Blind, Controlled, Phase IV Trial

[Arthritis Rheumatol. 2008;58:73-81.]

MTX naïve RA患者を対象とした,
MTX sc (15mg/w)とMTX po (15mg/w)の二重盲検RCT

- DAS28≧4のMTX naive RAをランダム化振り分け
  - **MTX sc群** (15mg/w)+ PC po (n=188): 24w
  - **MTX po群** (15mg/w)+ PC sc (n=187): 24w
- 16wでACR20を満たさない場合, po→sc, もしくはsc→20mg scとする.
- Primary outcome: 24wのACR20





- 24wで以下に有意差 (P<0.05)
- ACR20: sc 78%, po 70%
- ACR70: sc 41%, po 33%
- 罹病歴12M以上の方がscのACR20がより高い
- 副作用は同等

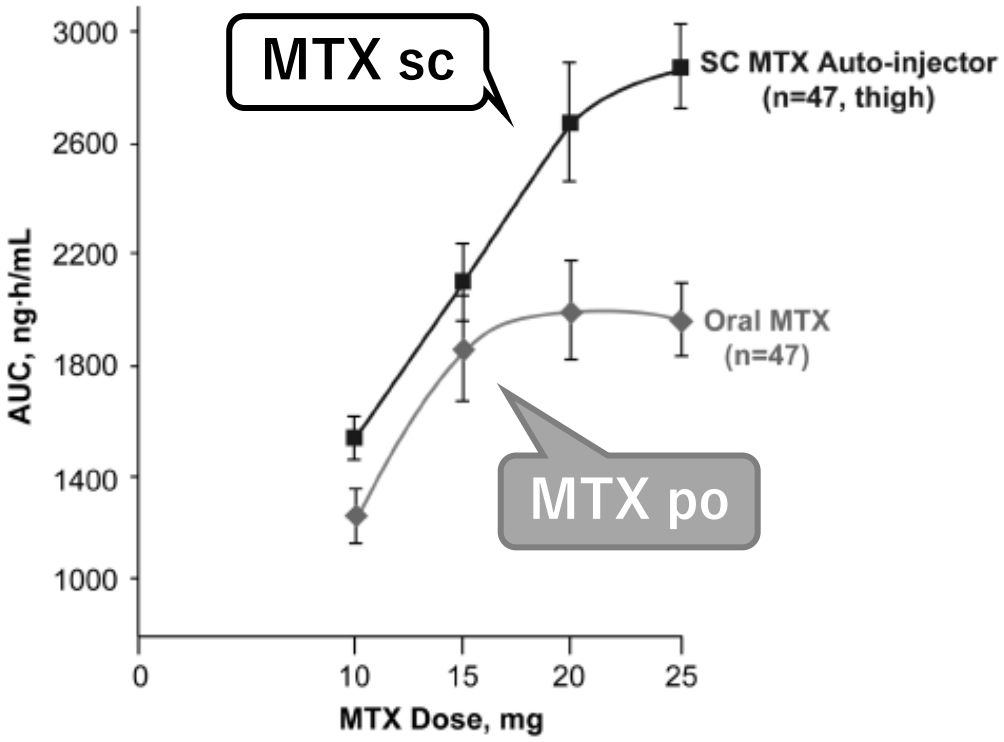
- **結論: MTX scは, 同量のMTX poより有効性が有意に高い**
- **忍容性に差はない.**

2014 RCT
MTX sc/po

Head-to-head, randomised, crossover study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis: drug-exposure limitations of oral methotrexate at doses ≥15 mg may be overcome with subcutaneous administration

[Ann Rheum Dis 2014;73:1549-51.]
NCT01618968

Michael H Schiff,[1] Jonathan S Jaffe,[2] Bruce Freundlich[3,4]

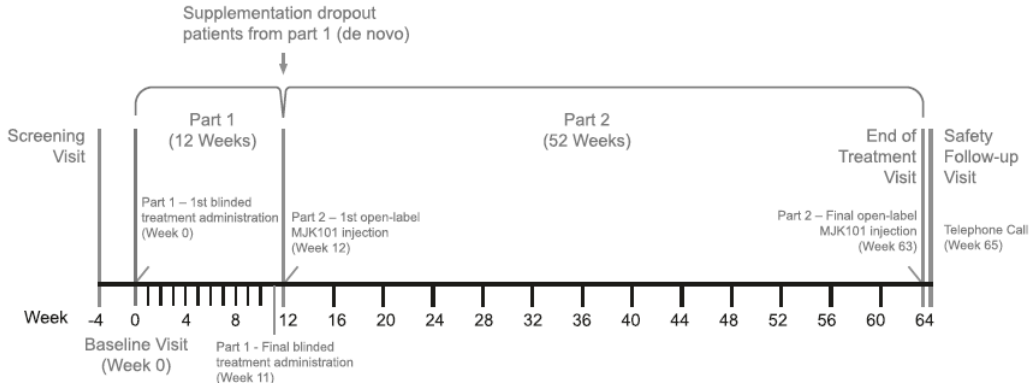


- MTX scとMTX poのランダム化比較試験（多施設参加, open-label）.
- MTX 10/15/20/25mgを, 経口・腹部sc・大腿scの3群にランダム化 (RA 47人), 投与24時間後の血中濃度/AUCを比較.
- MTX po: 15mg以上でAUCがプラトー.
- MTX sc: 15mg以上でもAUCが上昇.
- 予想しない有害事象は双方で認めず.
- 結論: MTX scは15mg/w以上でも曝露量が上昇するが, AEは増加しなかった.
- MTX poで効果不十分な場合, MTX scが選択肢となり得る.

方法

Part 1 (0-12週，二重盲検期)

- MTX-naïveのRA患者を1:1でランダム化.
  - **MTX 皮下注群 (n=53)**：7.5mg/週 (MJK101: Prefilled syringe)
  - **MTX 経口群 (n=50)**： 8mg/週
- Primary end point：12週のACR20



Part 2 (13-64週，継続投与期)

- 全員を皮下注群に組入れ, 52週間投与
- MTX 皮下注の量は 7.5→15mg/週まで2.5mg刻みに増量
  (DAS28-ESR<3.2とならない場合, 4週毎に増量)

結果：患者背景

- 男女比：１：４
- 年齢：平均 56.0歳
- 平均罹病期間：1.1カ月

- DAS28-ESR：5.72 vs 5.73
- HAQ-DI：1.12 vs 0.93
- CRP：1.65 vs 1.31

Table 1. Subject demographics and baseline characteristics by the treatment and total groups in Part 1.

Safety set	7.5 mg MJK101 ($N = 52$)	8 mg oral MTX ($N = 50$)	Total($N = 102$)
Sex			
Male	10 (19.2%)	10 (20.0%)	20 (19.6%)
Female	42 (80.8%)	40 (80.0%)	82 (80.4%)
Age (years)	57.8 (10.84)	54.1 (12.20)	56.0 (11.61)
Weight (kg)	60.60 (13.833)	59.85 (11.657)	60.23 (12.755)
BMI (kg/m^2)	23.37 (3.644)	23.83 (3.831)	23.60 (3.726)
Duration of RA (months)	1.329 (4.1481)	0.908 (1.5573)	1.123 (3.1480)
RF (IU/ml)	153.23 (194.905)	77.07 (99.509)	115.90 (159.530)
RF, >upper limit	46 (88.5%)	35 (70.0%)	81 (79.4%)
ACP antibodies (U/ml)	151.00 (186.367)	139.41 (184.932)	145.32 (184.836)
FAS	7.5 mg MJK101 ($N = 52$)	8 mg oral MTX ($N = 49$)	Difference (95% CI)/*p*-value
DAS28-ESR score	5.72 (1.121)	5.73 (1.031)	−0.01 (−0.44, 0.41)/.946
HAQ-DI score	1.12 (0.687)	0.93 (0.598)	0.19 (−0.06, 0.45)/.139
SJC (66)	13.04 (5.921)	13.45 (10.421)	−0.41 (−3.80, 2.97)/.810
TJC (68)	14.81 (8.916)	15.78 (11.433)	−0.97 (−5.00, 3.07)/.635
CRP (mg/dl)	1.65 (2.157)	1.31 (2.066)	0.34 (−0.50, 1.17)/0.425

結果：Part 1

- 12週での効果は皮下注は経口と同等（ACR20はscが高い [p=0.530]）
- 有害事象は皮下注の方が少なかった（特に消化器の副作用）

Table 2. ACR20, ACR50, and ACR70 response rates at Weeks 4, 8, and 12 in Part 1 (FAS).

	7.5 mg MJK101 ($N = 52$)n (%)	8 mg oral MTX ($N = 49$)n (%)	Difference in treatment proportions (95% CI)/p-value
ACR20 responders at			
Week 4	19 (36.5)	16 (32.7)	3.9 (–15.6, 23.3)/.729
Week 8	24 (46.2)	24 (49.0)	–2.8 (–22.4, 17.0)/.806
Week 12	31 (59.6)	25 (51.0)	8.6 (–11.3, 27.8)/.530
ACR50 responders at			
Week 4	4 (7.7)	4 (8.2)	–0.5 (–19.6, 19.2)/.997
Week 8	10 (19.2)	12 (24.5)	–5.3 (–24.8, 14.2)/.561
Week 12	14 (26.9)	12 (24.5)	2.4 (–17.3, 21.4)/.806
ACR70 responders at			
Week 4	1 (1.9)	2 (4.1)	–2.2 (–21.4, 17.5)/.598
Week 8	3 (5.8)	4 (8.2)	–2.4 (–21.4, 17.3)/.717
Week 12	5 (9.6)	8 (16.3)	–6.7 (–26.0, 13.1)/.362

Exact unconditional 95% CI is presented. The p-value (two-sided) is obtained from the exact test of zero risk difference. N: number of patients in the respective set; n: number of patients with the respective result.

Table 4. AEs by SOC and PT in Part 1—reported by >5% of patients in either treatment group (safety set).

SOC PT	7.5 mg MJK101 ($N = 52$)n (%) E	8 mg oral MTX ($N = 50$)n (%) E	Total($N = 102$)n (%) E
Any	30 (57.7) 49	36 (72.0) 81	66 (64.7) 130
GI disorders	8 (15.4) 9	17 (34.0) 24	25 (24.5) 33
Nausea	2 (3.8) 2	7 (14.0) 7	9 (8.8) 9
Stomatitis	3 (5.8) 3	3 (6.0) 3	6 (5.9) 6
Constipation	1 (1.9) 1	3 (6.0) 3	4 (3.9) 4
Diarrhoea	0	3 (6.0) 3	3 (2.9) 3
Infections and infestations	8 (15.4) 8	9 (18.0) 10	17 (16.7) 18
Nasopharyngitis	4 (7.7) 4	6 (12.0) 7	10 (9.8) 11
Musculoskeletal and connective tissue disorders	6 (11.5) 8	6 (12.0) 6	12 (11.8) 14
RA	4 (7.7) 4	3 (6.0) 3	7 (6.9) 7
Injury, poisoning, and procedural complications	6 (11.5) 6	1 (2.0) 1	7 (6.9) 7
Investigations	4 (7.7) 5	3 (6.0) 4	7 (6.9) 9
Skin and SC tissue disorders	3 (5.8) 3	4 (8.0) 7	7 (6.9) 10
Eczema	0	3 (6.0) 4	3 (2.9) 4
General disorders and administration site conditions	2 (3.8) 2	3 (6.0) 4	5 (4.9) 6
Nervous system disorders	1 (1.9) 2	4 (8.0) 5	5 (4.9) 7
Vascular disorders	3 (5.8) 3	2 (4.0) 2	5 (4.9) 5
Blood and lymphatic system disorders	0	4 (8.0) 4	4 (3.9) 4
Respiratory, thoracic, and mediastinal disorders	1 (1.9) 1	3 (6.0) 4	4 (3.9) 5
Hepatobiliary disorders	0	3 (6.0) 4	3 (2.9) 4
Metabolism and nutrition disorders	0	3 (6.0) 3	3 (2.9) 3

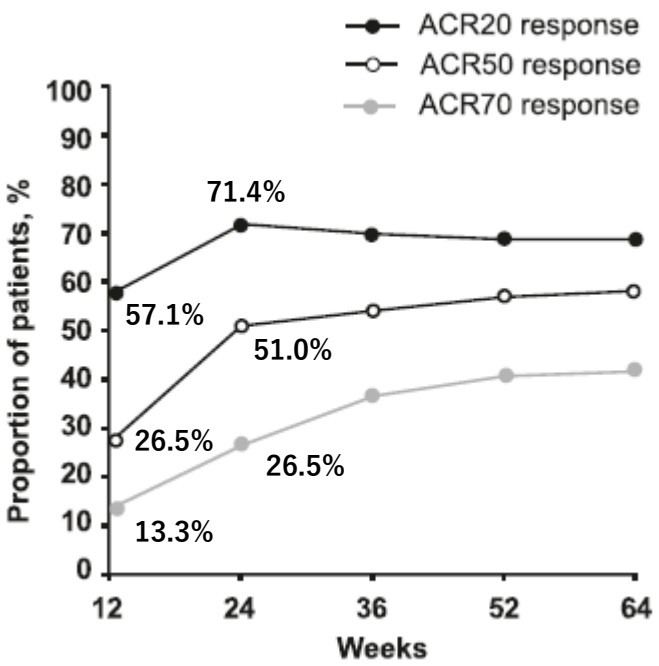
E: number of events; N: number of patients in the respective dose group; n: number of patients with the respective event.

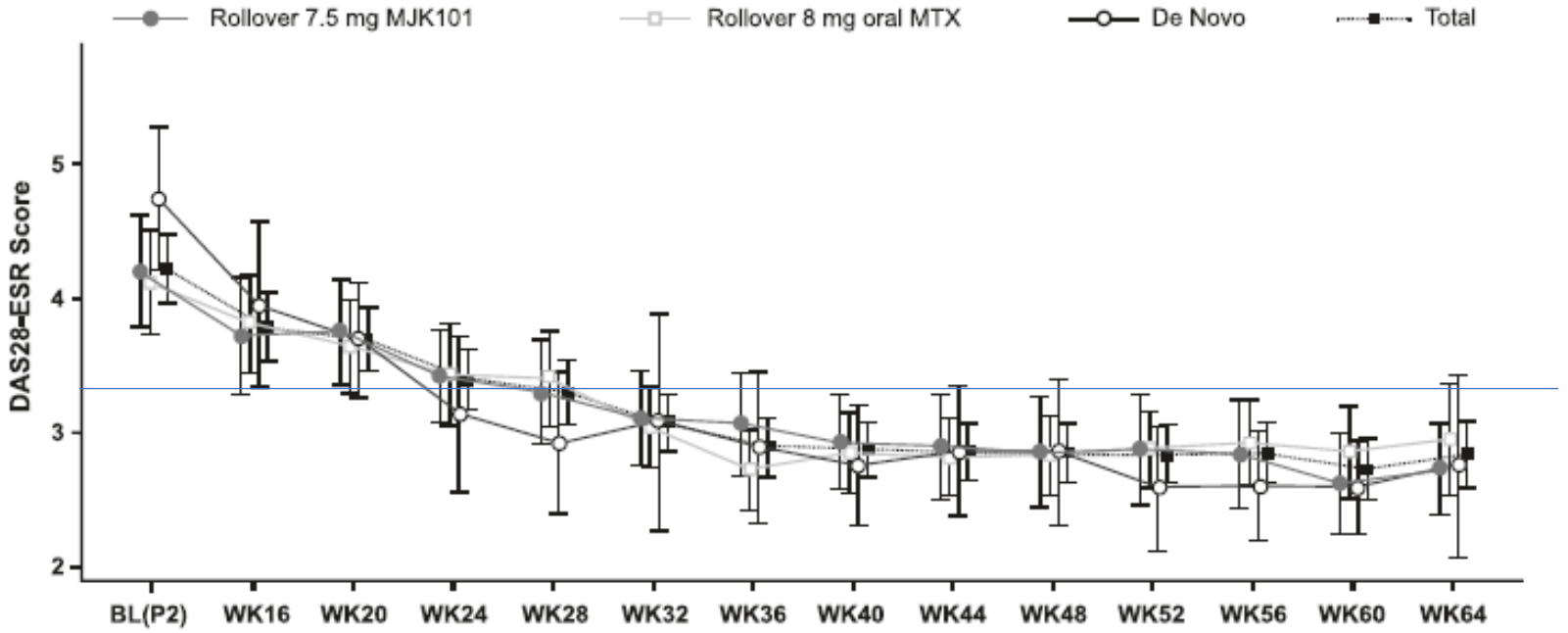
結果：Part 2

n = 23
Trial Discontinuation

Reasons:
- Adverse Event: 6
- Lost to Follow-up: 2
- Withdrawal by patient: 3
- Treatment Failure (according to the Investigator): 10
- Physician Decision: 2

- Rolloverを含めた長期経過は良好だった.
- 109人中23人中止 (有害事象 6人)も, 概ね忍容性は高かった.





結果：Part 2

- 全体の46.8%が15mg/wまで増量.
- 増量とともに，疾患コントロールは改善している.

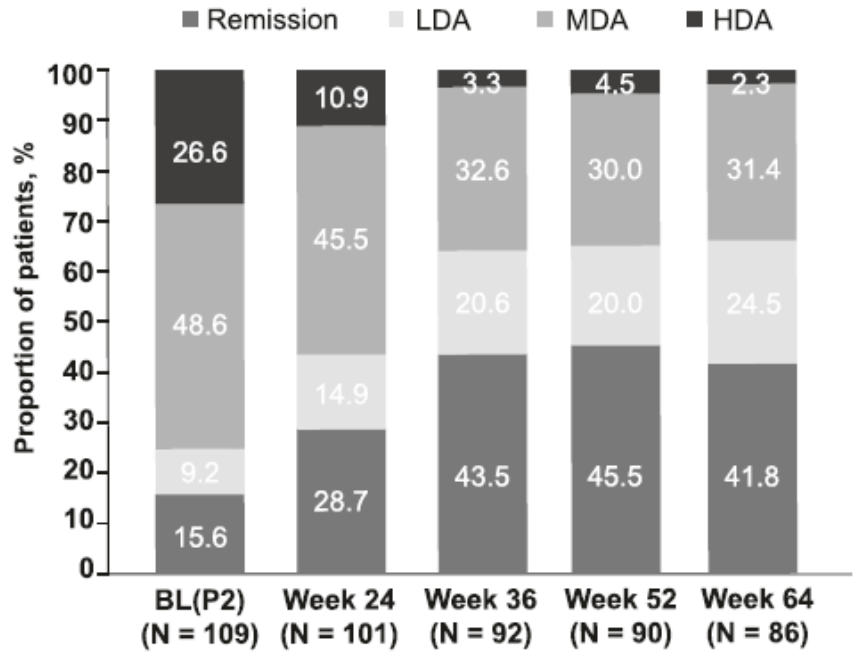


Table S8. Dose group by visit in totalgroup in Part 2 (safety set).

Total (N = 109) n (%)	Week 16	Week 20	Week 24	Week 36	Week 52	Week 64
7.5 mg	18 (16.5)	17 (15.6)	16 (14.7)	14 (12.8)	13 (11.9)	14 (12.8)
10 mg	87 (79.8)	24 (22.0)	17 (15.6)	16 (14.7)	12 (11.0)	9 (8.3)
12.5 mg	0	64 (58.7)	25 (22.9)	12 (11.0)	9 (8.3)	12 (11.0)
15 mg	0	0	44 (40.4)	52 (47.7)	56 (51.4)	51 (46.8)
Missing	4 (3.7)	4 (3.7)	7 (6.4)	15 (13.8)	19 (17.4)	23 (21.1)

N = number of patients on the intended set; n = number of patients within dose group.

結論

- MTX皮下注射（最大 15 mg/週）は，日本人集団において，長期にわたって効果的であり，良好な忍容性を示した.

- MTX皮下投与は，日本人のRA患者にとって有益な選択肢と考えられた.