METHOTREXATE IN THE REAL LIFE:

THE MARI STUDY

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MTX EFFICACY: MET NEEDS

Ann Rheum Dis 2009;**68**:1086–1093.

Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative

Reumatismo, 2013; 65 (5): 207-218

Systematic review of 2008-2012 literature and update of recommendations for the use of methotrexate in rheumatic diseases, with a focus on rheumatoid arthritis

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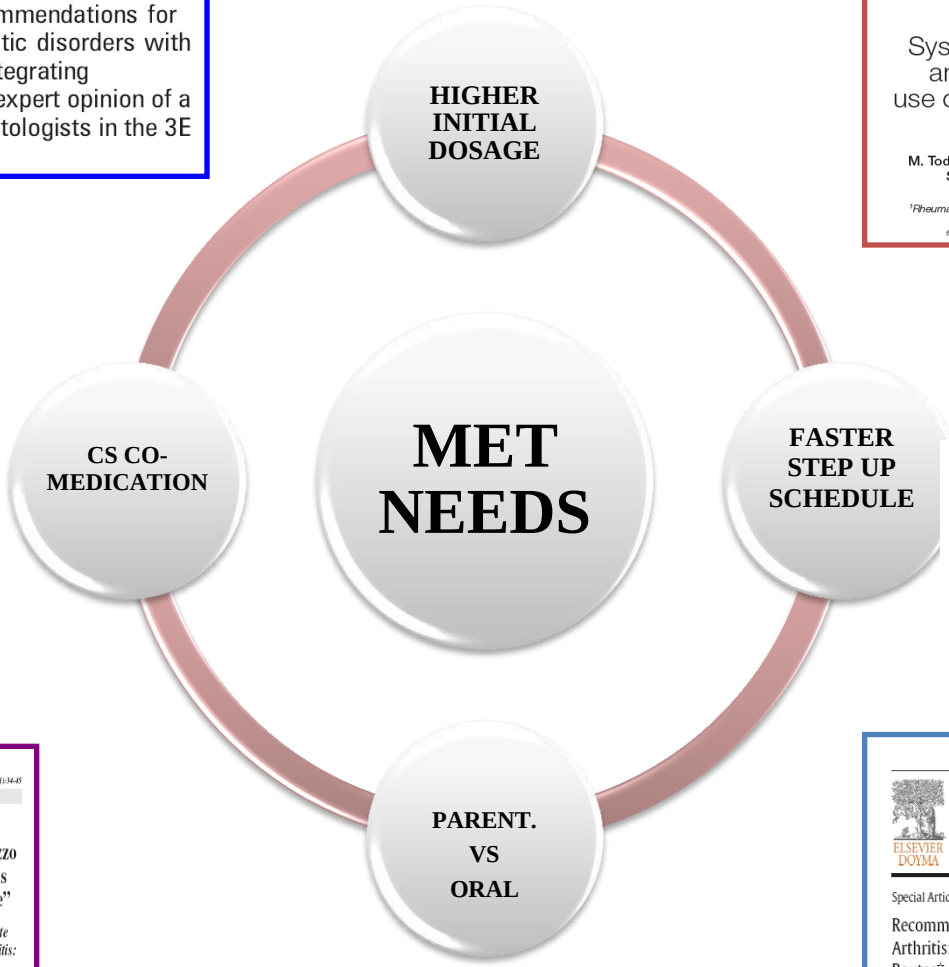

PRÁTICA CLÍNICA

ACTA REUMATOL PORT. 2009;34:78-95

RECOMENDAÇÕES PORTUGUESAS PARA UTILIZAÇÃO DE METOTREXATO NO TRATAMENTO DE DOENÇAS REUMÁTICAS

Reumatismo, 2010; 62(1):34-45

LAVORO ORIGINALE

Consensus italiana* sulle raccomandazioni per l'utilizzo del methotrexate nelle malattie reumatiche con focus sull'artrite reumatoide: i risultati della "3E initiative"

Italian consensus on the recommendations about the use of methotrexate for the treatment of rheumatic diseases with a focus on rheumatoid arthritis: results from the "3E initiative"

F. De Leonardis[1], S. Alivernini[2], E. Bonacci[3], A.M. Buono[4], S. Bombardieri[5], G.F. Ferraccioli[2], C. Montecucco[6], L. Sinigaglia[6], F. Trotta[1], G. Valentini[4]

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Reumatol Clin. 2015;11(1):3–8

Reumatología Clínica

www.reumatologiaclinica.org

Special Article

Recommendations for the Use of Methotrexate in Rheumatoid Arthritis: Up and Down Scaling of the Dose and Administration Routes☆

Jesús Tornero Molina,[a,*] Francisco Javier Ballina García,[b] Jaime Calvo Alén,[c] Miguel Ángel Caracuel Ruiz,[d] Jordi Carbonell Abelló,[e] Antonio López Meseguer,[f] José Vicente Moreno Muelas,[g] Trinidad Pérez Sandoval,[h] Jesús Quijada Carrera,[i] Pilar Trenor Larraz,[j] Antonio Zea Mendoza[k]

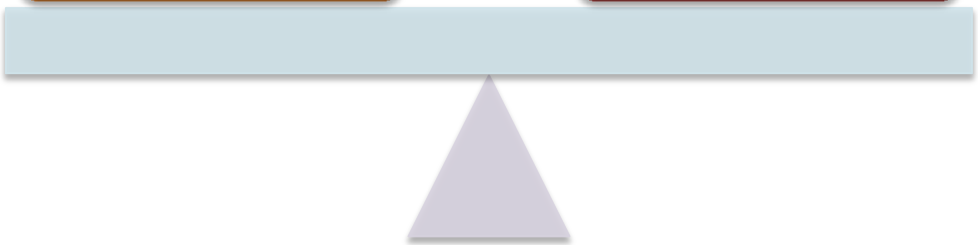
MTX EFFICACY: MET NEEDS

CLINICAL TRIALS/CTs

REAL LIFE DATA

CLINICAL TRIALS VS REAL LIFE DATA

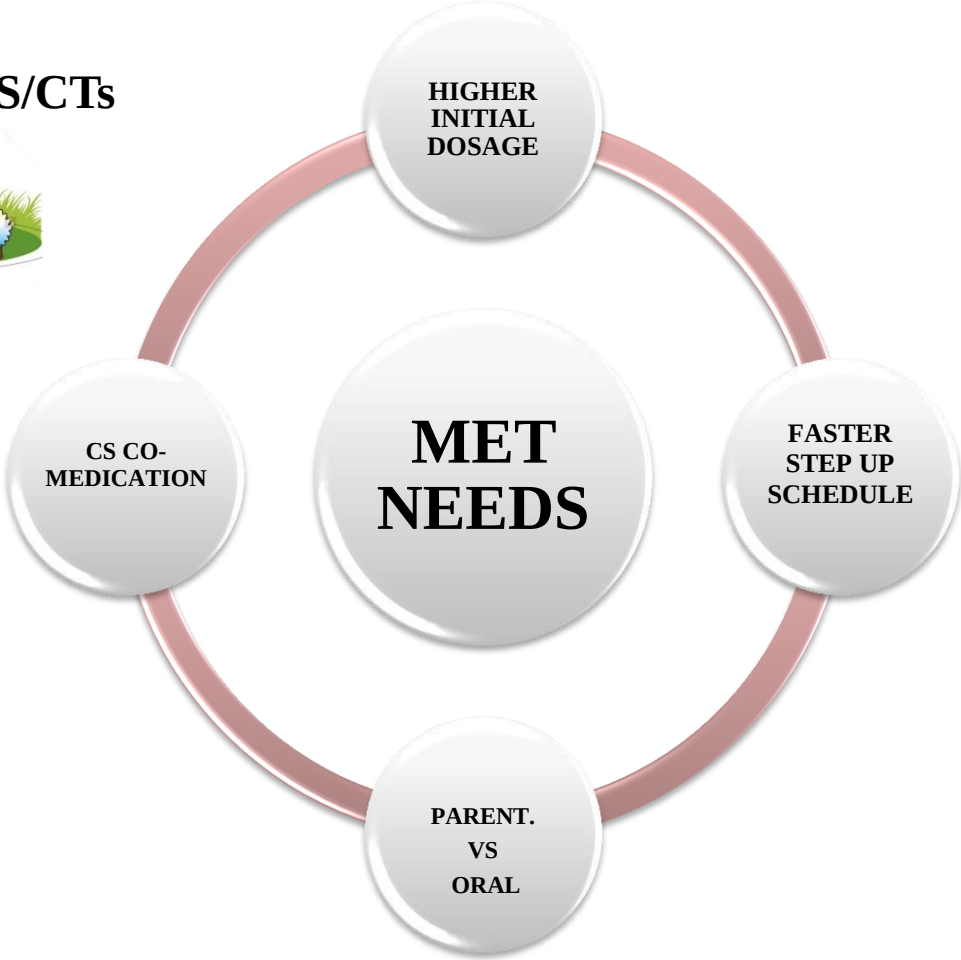
NON-EXPERIMENTAL DESIGN	EXPERIMENTAL DESIGN
Larger sample size and longer f-up	Best chance to see benefit
Uneven data captured	Strong internal validity, but scarse generalization
Real life patients	Outcomes defined and captured
Confounding by indication	Defined and balanced population



MTX EFFICACY: MET NEEDS

CLINICAL TRIALS/CTs

REAL LIFE DATA



MTX EFFICACY: MET NEEDS

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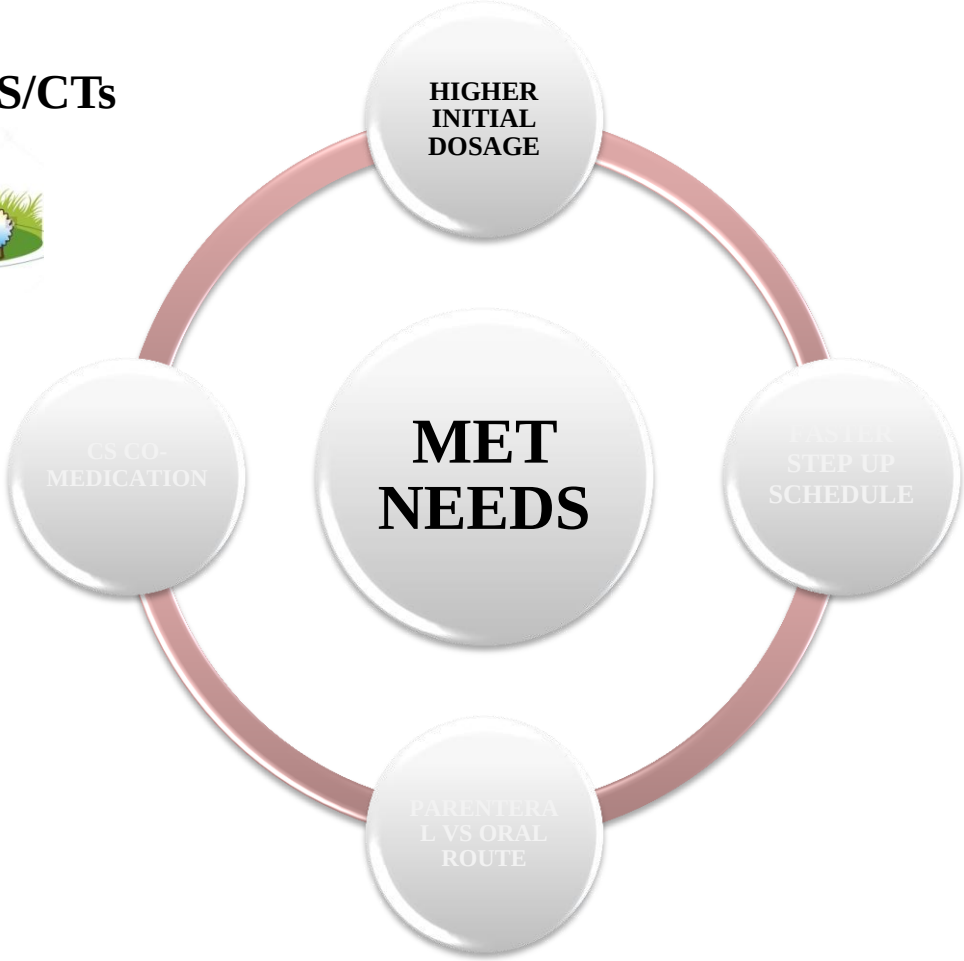

Optimal strategy from CTs
Initial dose: the higher, the better

Author, Publication year	Study design	N patients/ Population	Treatment strategies (MTX)	Results
Furst et al, 1989	RCT, double-blind 16 weeks	52 established RA DMARDs failure MTX naive	a) 5-10 mg/wk p.o. b) 12.5-20 mg/wk p.o. c) 25-35 mg/wk p.o. d) Placebo **No folic acid**	Significantly better control of disease activity in b) vs a). **Dose-dependent toxicity.** Similar toxicity in b) vs a); significantly higher in c.
Schnabel et al, 1994	RCT, open-label 52 weeks	185 established RA DMARDs failure MTX naive	a) 15 mg/wk p.o. b) 25 mg/wk p.o. **No folic acid**	27% in a) vs 3% in b) required higher dosage of MTX due to inefficacy. About 9% pz in a) e b) reduced MTX dosage for adverse events/toxicity.
Thompson et al, 1984	RCT, double-blind 6 weeks	48 established RA	a) Placebo b) 10 mg/wk i.m. c) 25 mg/wk i.m. **No folic acid**	At 6 weeks no significant differences for efficacy between two groups. **Dose-dependent toxicity.**

Optimal strategy from RLD
Initial dose: the higher, the better

Implementation of a Treat-to-Target Strategy in Very Early Rheumatoid Arthritis

Results of the Dutch Rheumatoid Arthritis Monitoring Remission Induction Cohort Study

Table 1. Treatment protocol*

Followup	DAS28	Medication
Week 0	≥2.6	MTX 15 mg/week
Week 8	≥2.6	MTX 25 mg/week
Week 12	≥2.6	MTX 25 mg/week + SSZ 2,000 mg/day
Week 20	≥2.6	MTX 25 mg/week + SSZ 3,000 mg/day
Week 24	≥3.2†	MTX 25 mg/week + ADA 40 mg every 2 weeks
Week 36	≥2.6 and decrease of >1.2‡	MTX 25 mg/week + ADA 40 mg/week
Week 52	≥3.2†	MTX 25 mg/week + etan. 50 mg/week
1 year + 3 months	≥3.2†	MTX 25 mg/week + inflix. 3 mg/kg every 8 weeks (after a loading dose at weeks 0, 2, and 6)
1 year + 6 months	≥2.6 and decrease of >1.2‡	MTX 25 mg/week + inflix. 3 mg/kg every 4 weeks

AIM: intensified T2T MTX-based approach

TARGET POPULATION: "very early" RA (< 1 year) from DREAM cohort

Goal: clinical endpoints at 1 year

Vermeer M, et al. Arthritis Rheum 2011

Optimal strategy from RLD
Initial dose: the higher, the better

Table 3. Clinical outcomes in the patients after 6 months and 12 months of followup*

	6 months (n = 491)	12 months (n = 389)
DAS28 level		
Remission (DAS28 <2.6)	231 (47.0)	226 (58.1)
Low (2.6 ≤ DAS28 ≤ 3.2)	95 (19.4)	57 (14.7)
Moderate (3.2 < DAS28 ≤ 5.1)	143 (29.1)	97 (24.9)
High (DAS28 >5.1)	22 (4.5)	9 (2.3)
EULAR response		
Good	283 (57.6)	264 (67.9)
Moderate	139 (28.3)	93 (23.9)
None	69 (14.1)	32 (8.2)
ACR remission	123/384 (32.0)	149/321 (46.4)

* Values are the number (%). American College of Rheumatology (ACR) remission could not be evaluated in all patients due to missing values for morning stiffness. DAS28 = Disease Activity Score in 28 joints; EULAR = European League Against Rheumatism.

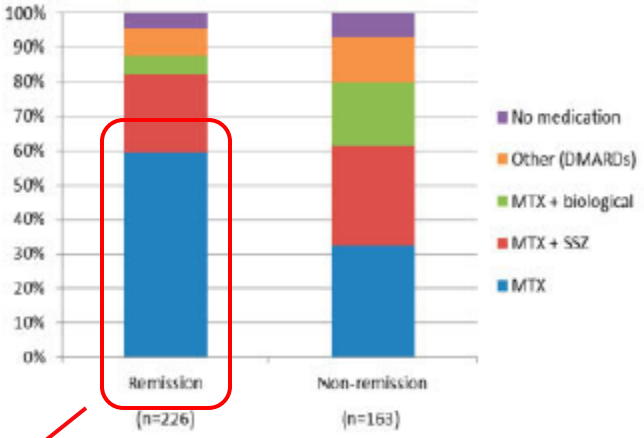

Figure 2. Actual medication use, stratified for the presence or absence of remission (defined as a Disease Activity Score in 28 joints of <2.6) after 12 months of followup. Other (disease-modifying antirheumatic drugs [DMARDs]) treatment consisted mainly of either monotherapy or combination therapy with methotrexate (MTX), hydroxychloroquine, or sulfasalazine (SSZ).

A 12 months among pts in DAS28 clinical remission, 59.3% was on MTX only

Vermeer M, et al. Arthritis Rheum 2011

Sustained Beneficial Effects of a Protocolized Treat-to-Target Strategy in Very Early Rheumatoid Arthritis: Three-Year Results of the Dutch Rheumatoid Arthritis Monitoring Remission Induction Cohort

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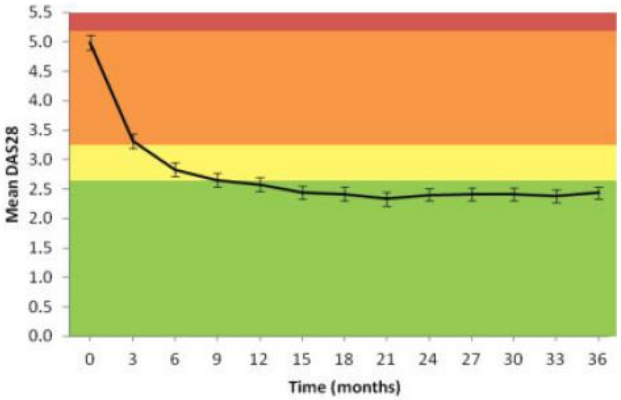
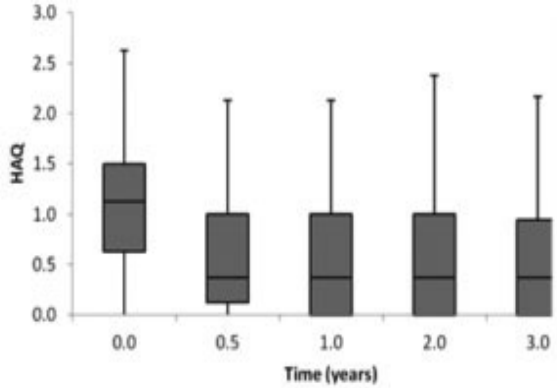
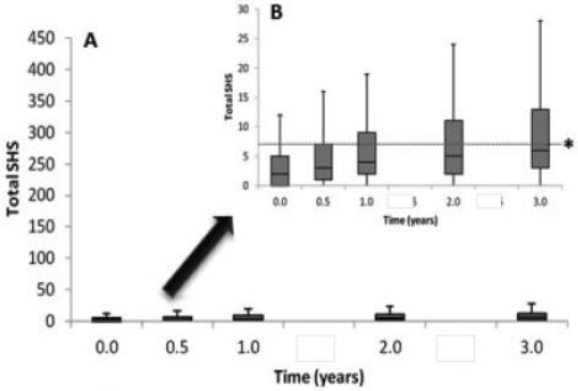
A. E. VAN DER BIJL,[4] P. L. C. M. VAN RIEL,[5] AND M. A. F. J. VAN DE LAAR[1]







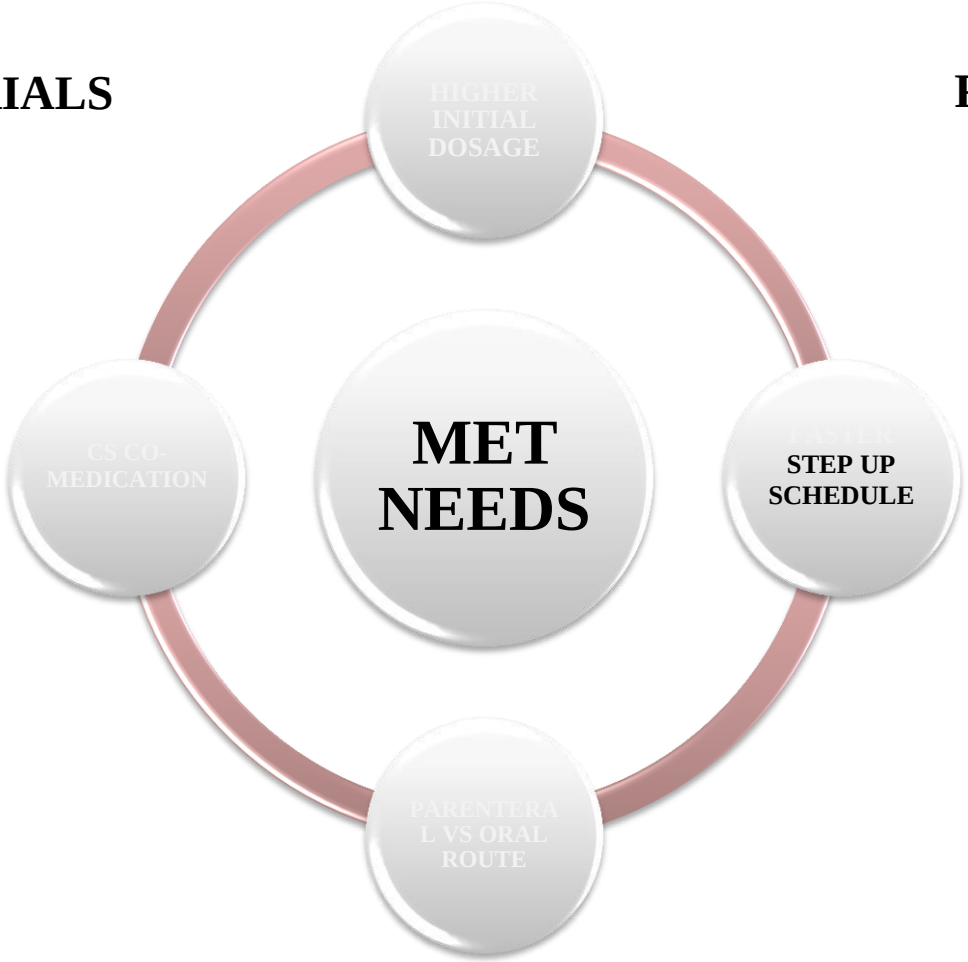
Benefits have been maintained up to 3 years of follow up

Vermeer M, et al. Arth Care Res 2013

MTX EFFICACY: MET NEEDS

CLINICAL TRIALS

REAL LIFE DATA



Optimal strategy from CTs
Step up: the faster, the better

Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial)

S M M Verstappen, J W G Jacobs, M J van der Veen, A H M Heurkens, Y Schenk, E J ter Borg, A A M Blaauw, J W J Bijlsma, on behalf of the Utrecht Rheumatoid Arthritis Cohort study group

See linked editorial p1409

Ann Rheum Dis 2007;**66**:1443–1449. doi: 10.1136/ard.2007.071092

	Response compared to previous visit:	Inadequate response	Sustained response
Intensive strategy group	>20% improvement of number of swollen joints and >20% improvement in 2 out of 3 criteria: ESR, number of tender joints, and VAS general well-being.	≤50% improvement from baseline for number of swollen joints and ≤50% improvement from baseline for 2 out of 3 variables: ESR, number of tender joints, and VAS general well-being.	No swollen joints and 2 out of 3 criteria: number of painful joints ≤3, ESR ≤20 mm/h^{1st}, VAS general well being ≤20 mm.
Conventional strategy group	- Decrease of number of swollen joints - If number of swollen joints unchanged, decision of response depended on assessors' judgment, looking at number of tender joints, ESR, and VAS general well-being.	Number of swollen joints ≥6, number of painful joints ≥3 , ESR ≥28 mm/h^{1st}, and morning stiffness ≥45 min.	

TRIAL DESIGN: open label multicenter RCT, 2 years of f-up
TARGET POPULATION: 299 early RA, DMARDs naive
TREATMENT: starting MTX dosage 7.5 mg/wk
ALLOCATION:
1) INTENSIVE ARM: +5mg/wk every month
vs
2) CONVENTIONAL ARM: +5 mg/wk every 3 months

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PRIMARY END-POINTYS

TRIAL DESIGN	TARGET POPULATION	TREATMENT	END POINTS
Open-label Multicentric RCT	299 early RA DMARDs naive Follow up: 2 years	a) "intensive" arm: 7,5 mg/wk p.o. + 5 mg/wk a months b) "conventional" arm: 7,5 mg/wk p.o. + 5 mg/wk every 3 months + folic acid	ACR50 OR: 1.8 (CI95% 1.1-2.8) AE OR: 2.3* (CI95% 1.02-5.3) No significant difference in structural progression.

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Increase by 5mg/month

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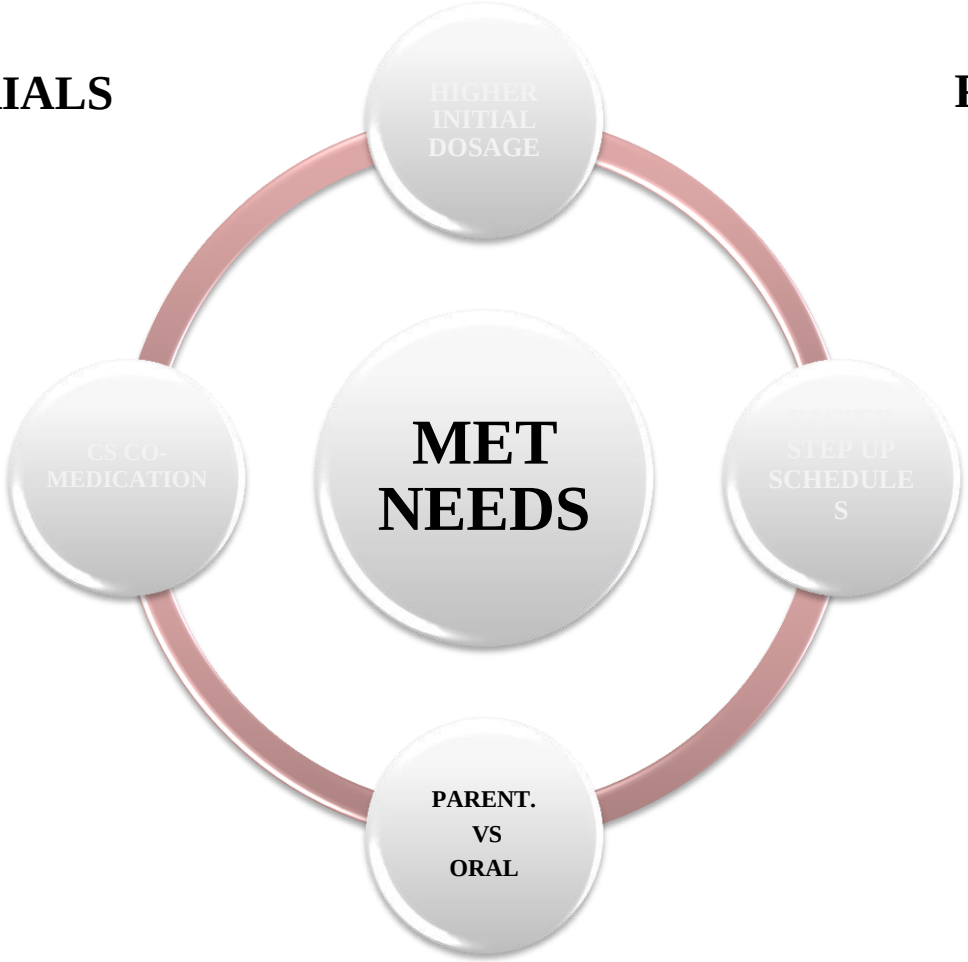
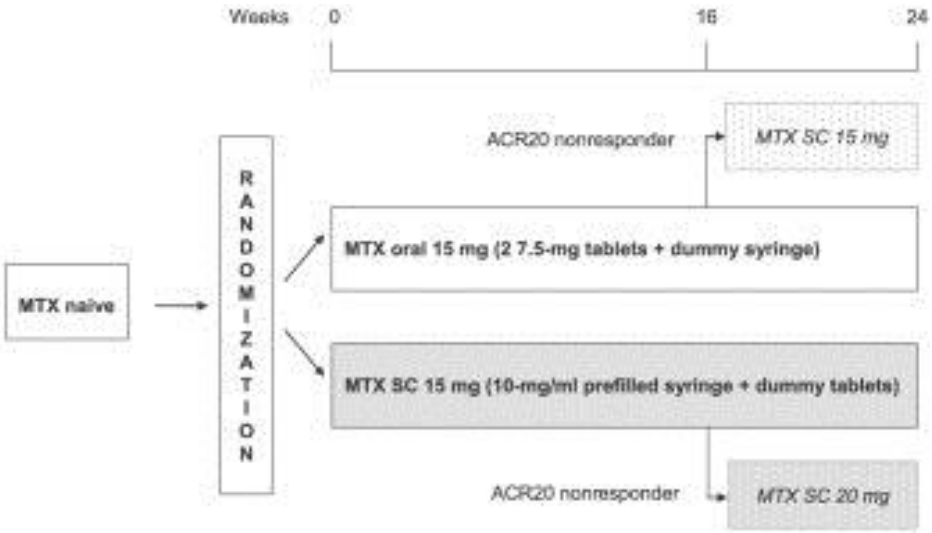
MTX EFFICACY: MET NEEDS

CLINICAL TRIALS

REAL LIFE DATA



Optimal strategy from CTs
Parenteral vs oral route: ab initio



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

P: 384 **early AR**, DAS28>4, **MTX naïve**, DMARDs naive (75%): 194 MTX SC, 190 MTX OS

switch 15 mg/wk OS > 15 mg/wk SC
vs
15 mg/wk SC > 20 mg/wk SC

Braun J, et al. Arthritis Rheum 2008

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

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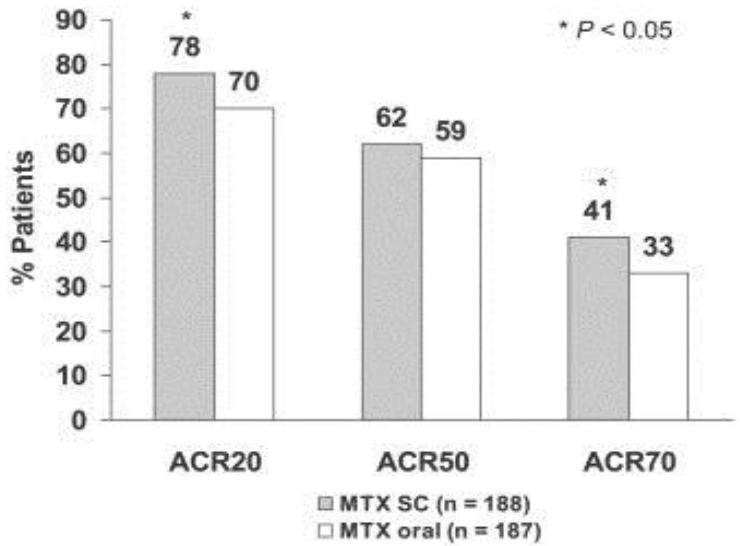
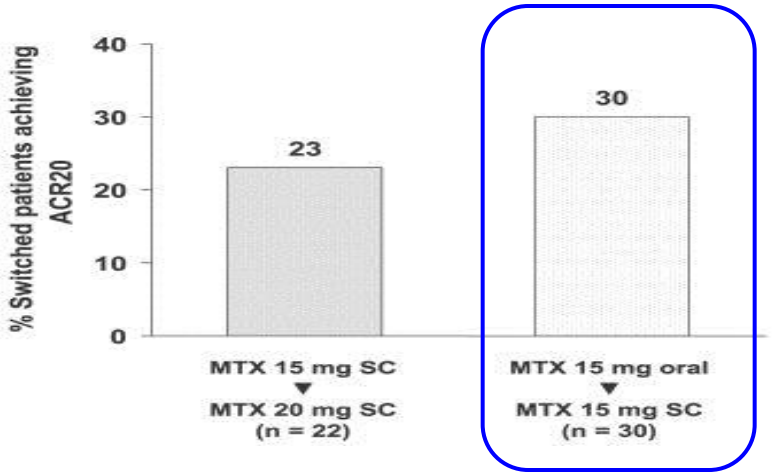


ACR20 responses significantly differed from 16 weeks forehead:
85% vs 77% (*p*< 0.05)

At 24 weeks: 78% vs 70% per MTX SC versus MTX OS (*p*< 0.05)

Braun J, et al. Arthritis Rheum 2008

Optimal strategy
Parenteral vs oral route: switch



At 16 weeks, 52 patients (14%) were ACR20 non-responders:

By changing route of administration (15 mg OS>15 mg SC): ACR20 in further **30% patients.**

By increasing the dosage (15 mg a 20 mg SC): ACR20 in further **23% patients**.

Braun J, et al. Arthritis Rheum 2008

Optimal strategy from RLD
Parenteral vs oral route: ab initio

The comparative effectiveness of oral versus subcutaneous methotrexate for the treatment of early rheumatoid arthritis

Hazlewood GS, *et al*. *Ann Rheum Dis* 2015;0:1–6.

Early RA patients from the The Canadian Early Arthritis Cohort (CATCH): multicentre, prospective, observational study of patients with ERA.

The choice of route of MTX (subcutaneous or oral) was at the discretion of the treating rheumatologist.

Table 1 Demographic and clinical characteristics of patients at baseline

Characteristic	Oral MTX (n=417)	Subcutaneous MTX (n=249)	p Value
Age, years	54 (14)	51 (15)	0.068
Female, %	75.1	73.1	0.57
Number of comorbidities (0–13)	2.2 (1.8)	2.5 (1.9)	0.041
Smoking status, %			0.28
Never smoked	39.1	45.4	
Ex-smoker	42.2	38.2	
Current smoker	18.7	16.5	
Education, %			0.23
Less than high school	10.1	5.6	
High school	36.0	39.8	
College or trade school	28.8	27.7	
University bachelors	17.0	19.7	
Other	8.2	7.2	
Symptom duration, months	5.2 (2.7)	5.2 (2.8)	0.61
Seropositive (RF or ACPA), %	78.8	82.0	0.35
Erosions present on hand or foot X-rays, %	24.4	31.1	0.08
HAQ-DI (0–3)	1.1 (0.69)	1.1 (0.69)	0.52
DAS-28	5.5 (1.4)	5.5 (1.4)	0.86
Starting dose of MTX, mg	17.2 (3.8)	22.3 (3.6)	<0.001
>20, %	5.0	45.2	
15–20, %	56.8	27.8	
<15, %	38.1	27.0	
Concurrent use of systemic glucocorticoids	48.0	51.8	0.34
Oral, %	24.2	13.7	0.001
Intramuscular or intra-articular, %	27.8	41.4	<0.001
Concurrent use of other DMARDs, %	53.0	42.6	0.009
Concurrent use of biological therapy, %	2.2	0.4	0.071

Optimal strategy from RLD
Parenteral vs oral route: ab initio

The comparative effectiveness of oral versus subcutaneous methotrexate for the treatment of early rheumatoid arthritis

Hazlewood GS, *et al*. *Ann Rheum Dis* 2015;0:1–6.

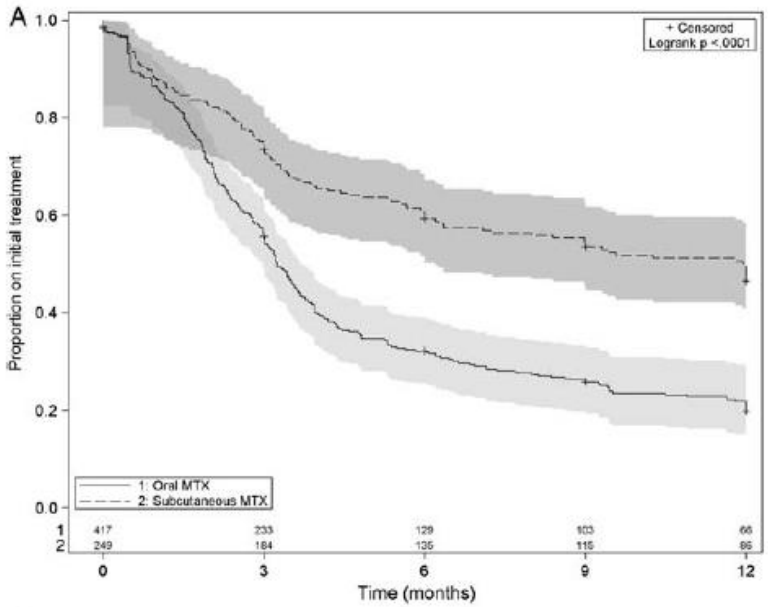


Table 3 Treatment failure by reason, unadjusted (%)

	Subcutaneous methotrexate	Oral methotrexate	p Value (χ^2)
Total treatment failures	49	77	<0.001
Inefficacy only	28	59	<0.001
Toxicity* only	3	2	0.63
Both inefficacy and toxicity*	18	16	0.57

*Toxicity was defined as physician documented side effects resulting in change in therapy.

At 1 year, 49% SC versus 77% oral MTX patients had changed treatment.

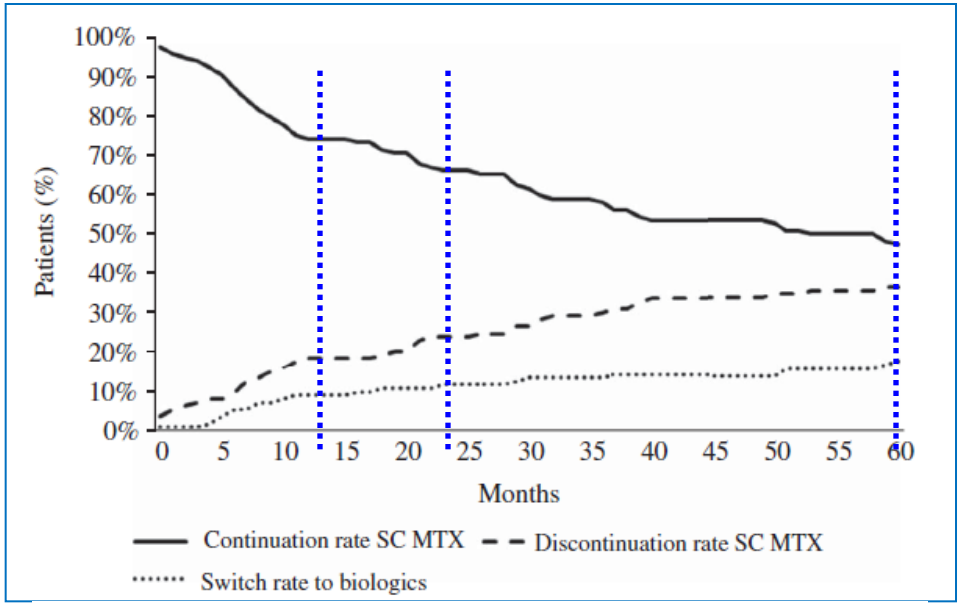
Optimal strategy from RLD Parenteral vs oral route: switch

Scand J Rheumatol 2014;iFirst article:1–7 1

Retrospective evaluation of continuation rates following a switch to subcutaneous methotrexate in rheumatoid arthritis patients failing to respond to or tolerate oral methotrexate: the MENTOR study

DGI Scott, P Claydon, C Ellis

Norfolk and Norwich University Hospital, Norwich, UK



MTX during the 5-year period, with a further 19 (17.0%) patients being switched to a biologic. Of note, almost half the patients who discontinued or were switched did so in the first 12 months of SC MTX therapy.

At 1 year after the OS>SC switch, the mean retention rate on SC MTX was **83,0%**.

At 2 year after the OS>SC switch, the mean retention rate on SC MTX was **75,2%.**

At 5 year after the OS>SC switch, the mean retention rate on SC MTX was **47%.**

Less than 10% patients started bDMARDs within the first year of follow up.

Adv Ther
DOI 10.1007/s12325-016-0295-8

REVIEW

Methotrexate and Rheumatoid Arthritis: Current Evidence Regarding Subcutaneous Versus Oral Routes of Administration

Gerolamo Bianchi · Roberto Caporali · Monica Todoerti · Paolo Mattana

Ab initio

Table 4 Differences in clinical response between MTX SC and MTX OR

Outcome	Duration of therapy, months[a]	MTX SC	MTX OR	*P* value	References
ACR20, %	6	78%	70%	<0.05	Braun et al. [14]
ACR70, %	6	41%	33%	<0.05	
DAS28, mean (SD)	3	3.49 (1.50)	3.92 (1.48)	0.002	Hazlewood et al. [21]
DAS28, mean (SD)	6	3.12 (1.46)	3.50 (1.51)	0.011	
DAS28, mean (SD)	9	2.79 (1.37)	3.23 (1.53)	0.005	
Change of therapy, %	12	49%	77%	<0.001	Hazlewood et al. [21]

Clinical trials

Real life

After switch

Table 5 Clinical response in patients switched from MTX OR to MTX SC because of treatment failure (inefficacy or toxicity)

Outcome	Duration of therapy, months	MTX SC	References
ACR20, %	2	30	Braun et al. [14]
Mean reduction in DAS28 score	1	0.3	Bakker et al. [15]
	4	0.5	
DAS28 reduction of ≥1.2 points, %	6	74	Mainmann et al. [16]
DAS28 score <3.2, %	6	29	
Improvement of DAS28, %	4	63	Bakker et al. [15]
Continuation rate, %	12	83	Scott et al. [17]
	24	75	
	60	47	
Additional biologic therapy, %	12	5.2	Scott et al. [17]
	24	8.5	

Clinical trials

Real life

Clinical trials

Real life

Adv Ther
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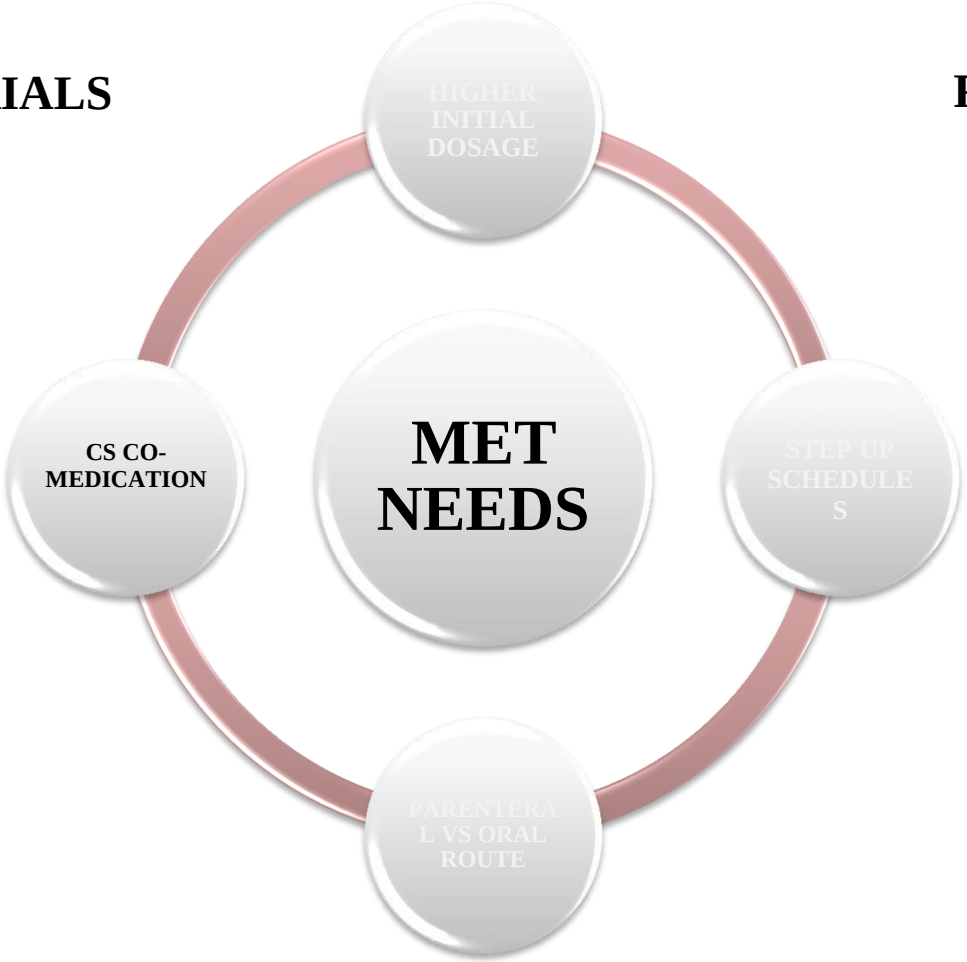
MTX EFFICACY: MET NEEDS

CLINICAL TRIALS

REAL LIFE DATA



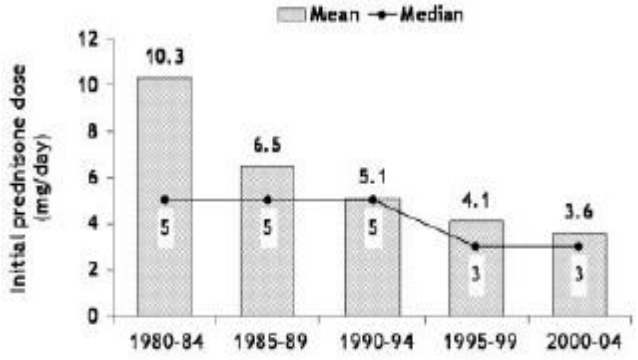
Optimal strategy from CTs CS-comedication

Author, Journal	Target population	DMARDs (MTX)	Steroids	End points	Results
Svensson, AR 2005	250 early AR (<1 year)	**In PDN: 50% MTX,** 35% SSZ; **In no-PDN: 53% MTX,** 37% SSZ.	**PDN 7.5 mg/d**	X-Ray and DAS28 at 2 years	At 2 years significantly less erosive score and new erosions in PDN-arm vs no-PDN arm. **DAS28 inter-group difference already significant at 3 months of follow up in favour of PDN.**
Wassenberg, AR 2005	166 early AR (<2 years)	**In PDN: 34% MTX,** 66% OS **In no-PDN: 41% MTX,** 59% OS	**PDN 5 mg/d**	Clinical, functional and structural outcomes at 2 years	**At 2 years significantly less structural damage, along with greater clinical and functional benefits in PDN arm.**
Bakker, AIM 2012	236 early AR (<1 year)	100 % pz: MTX (10 mg/s>30 mg/s)	**PDN 10 mg/d**	X-Ray at 2 years ACR/EULAR responses at 1 and 2 years	**Significantly less erosive score in PDN at 2 years.** **ACR responses significantly more frequent in PDN vs no-PDN.**
Montecucco, ART 2012	220 early AR (<1 anno)	100% MTX	**PDN 6.25 mg/d**	Clinical and US outomes at 12 months.	At 1 year significantly higher probability of clinical and US remission in PDN: RR 1.61 (CI95% 1.08,2.04) and RR 1.31 (CI95% 1.04,1.64), respectively.

Optimal strategy from RLD CS-comedication

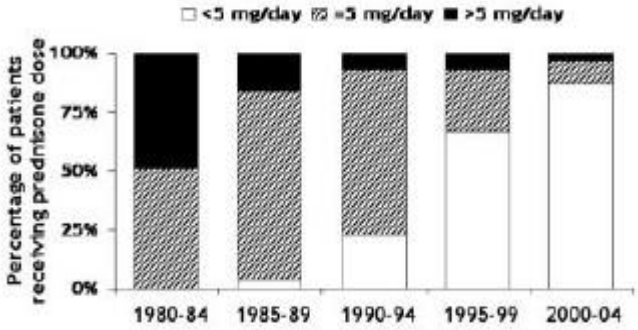
Decline of Mean Initial Prednisone Dosage From 10.3 to 3.6 mg/day to Treat Rheumatoid Arthritis Between 1980 and 2004 in One Clinical Setting, With Long-Term Effectiveness of Dosages Less Than 5 mg/day

THEODORE PINCUS,[1] TUULIKKI SOKKA,[2] ISABEL CASTREJÓN,[1] AND MAURIZIO CUTOLO[3]



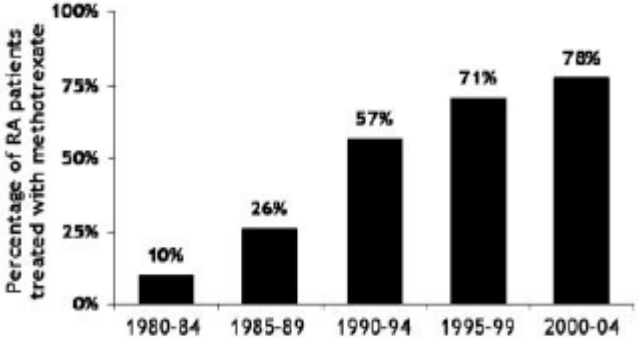
A

Decline in mean initial prednisone dosage



B

Decline in patients taking moderate-high CS



C

Increase in MTX users

Pincus T, et al. Arthritis Care Res 2013

progetto

MARI

Metotrexato nella terapia
dell' **A**rtrite
Reumatoide
in **I**talia

progetto MARI Metotrexato nella terapia dell'Artrite Reumatoide in Italia

Suboptimal methotrexate use in rheumatoid arthritis patients in Italy: the MARI study

L. Idolazzi[1], S. Adami[1], R. Capozza[2], G. Bianchi[3], A. Cozzolongo[4], O. Epis[5], E. Fusaro[6], G. Lapadula[7], A. Migliore[8], R. Pellerito[9], A. Pucino[10], L. Sinigaglia[11], E. Visalli[12], M. Rossini[1]

Clinical and Experimental Rheumatology 2015; **33**: 895-899.

DESIGN: multicenter observational retrospective study

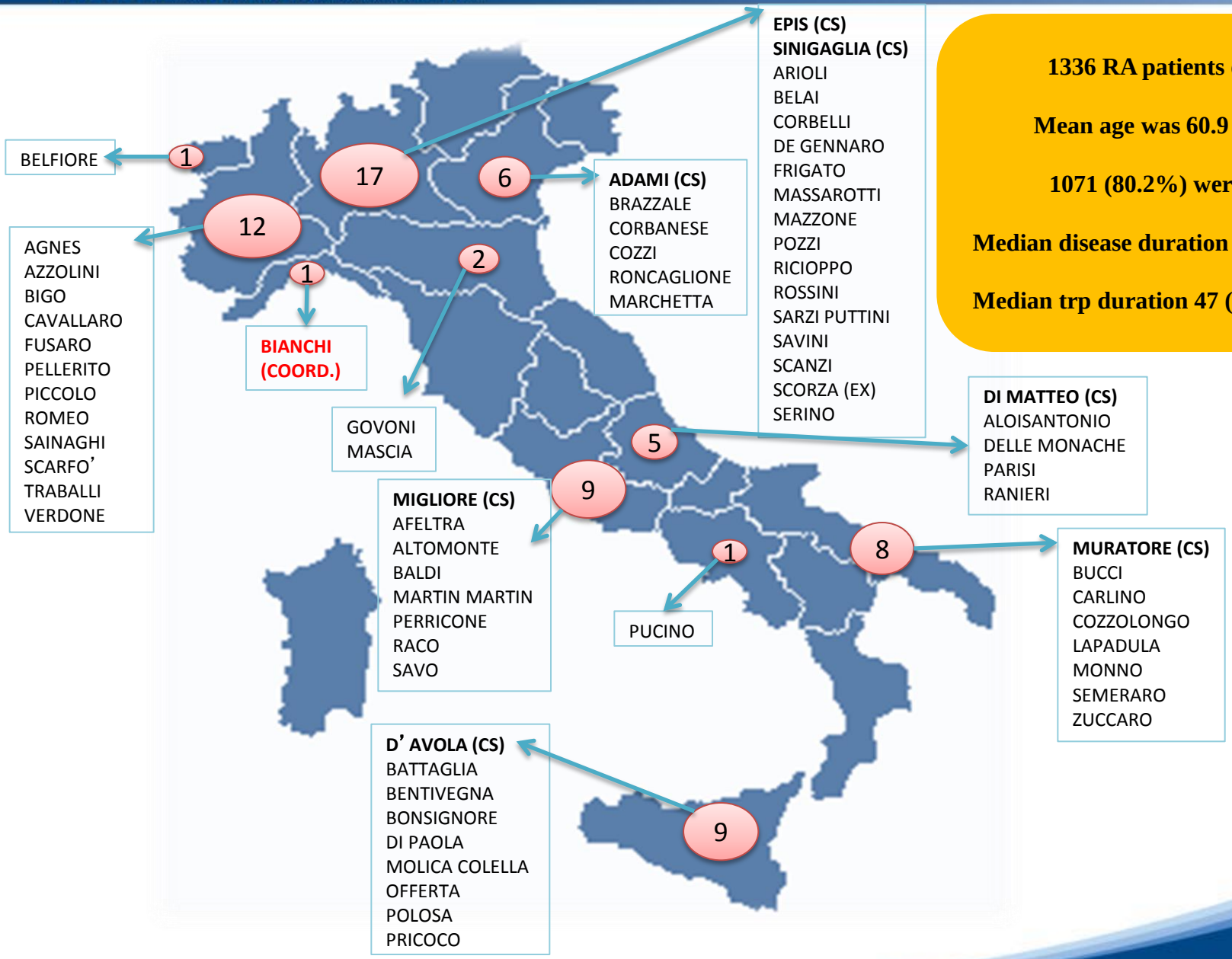
POPULATION: Italian RA patients (ACR 1987) on MTX treatment for at least 12 months over 60 Rheumatologic Units in Italy (December 2011-October 2013)

AIMS:

- cross-sectional analysis about patients' and disease characteristics, MTX prescription habits

progetto MARI Metotrexato nella terapia dell'Artrite Reumatoide in Italia

INVOLVED UNITS: 60



1336 RA patients on MTX.

Mean age was 60.9 (SD: 12.7)

1071 (80.2%) were women

Median disease duration 6 (IQR: 3,13) ys

Median trp duration 47 (IQR: 22,88) mts

PATIENTS' CHARACTERISTICS AT ENROLLMENT

	Oral (n=288)	Parenteral (n=1039)	
Female	80.5%	80.1%	ns
Postmenopausal	61.8%	61.5%	ns
Smoker	15.3%	14.8%	ns
Age	62.7 ± 13.4	61.0 ± 12.4	ns
Body weight	66.9 ± 13.7	68.7 ± 13.4	ns
Height	162.5 ± 8.1	163.5 ± 7.9	ns
Years since diagnosis	11 (1-25)	9 (1-14)	0.04
Initial oral daily dose of PN equivalent steroids			
None	22.6%	18.8%	ns
≤10 mg	65.3%	69.9%	
>10 mg	12.2%	10.9%	
Current oral daily dose of PN equivalent steroids			
None	55.9%	51.4%	0.003
≤5 mg	41.7%	41.7%	
>5 mg	2.4%	6.9%	
Other DMARDs			
HCQ	35.1%	26.7%	0.006
SSZ	3.8%	4.2%	
LFN	2.4%	3.9%	
CYC	2.4%	3.9%	0.05
Biological therapy	30.6%	32.7%	ns
AINS or analgesics	60.1%	58.4%	ns
Clinical assessment			
Patient VAS	6.0 ± 11.5	5.4 ± 11.5	0.003
Physician VAS	4.1 ± 8.4	4.4 ± 7.3	ns
DAS28	2.29 ± 0.96	2.51 ± 1.04	0.026
DAS28 <2.6	64.1%	56.6%	0.014
Bone erosion	52.4%	58.7%	0.034
Extra-articular manifestations	3.5%	5.4%	ns
Positive RF test	61.5%	64.4%	ns
ACPA-positive	51.4%	56.4%	ns

Parenteral route for patients with more severe disease:

- significantly higher mean DAS28,
- lower proportion of patients on DAS28 remission (<2.6),
- more frequent erosive features
- more associated prescription of other DMARDs .

MODALITIES OF MTX PRESCRIPTIONS: AT THE BEGINNING

1) TIME OF INTRODUCTION

2) INITIAL DOSAGE

3) INITIAL ROUTE OF ADMINISTRATION

4) THERAPEUTIC MODIFICATION AFTER 12 MONTHS (1049 pts)

1) LAG TIME TO MTX

MTX treatment began within 12 months of disease onset in 79% of the patients, with no significant differences between groups.

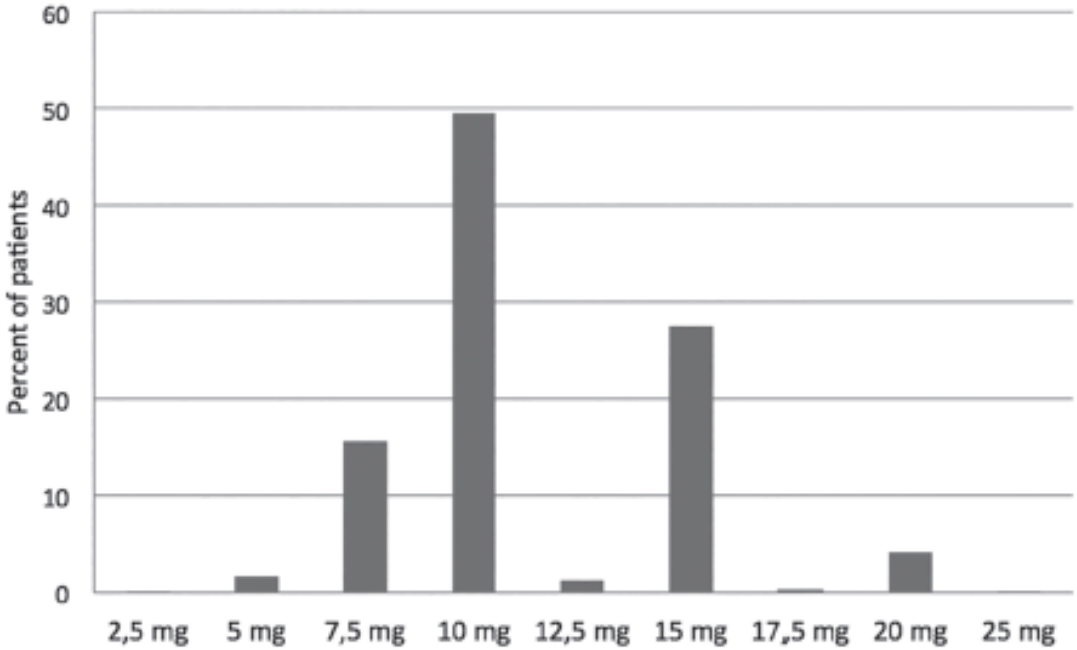
	Oral	Parenteral	*p*-value
Beginning of MTX treatment			
At disease onset	15.6%	18.1%	ns
Within 3–6 months	12.2%	16.3%	
Within 7–12 months	53.5%	46.7%	
Within >12 months	18.1%	18.6%	

2) INITIAL DOSE

Mean initial MTX dosage was significantly higher in the parenteral group.

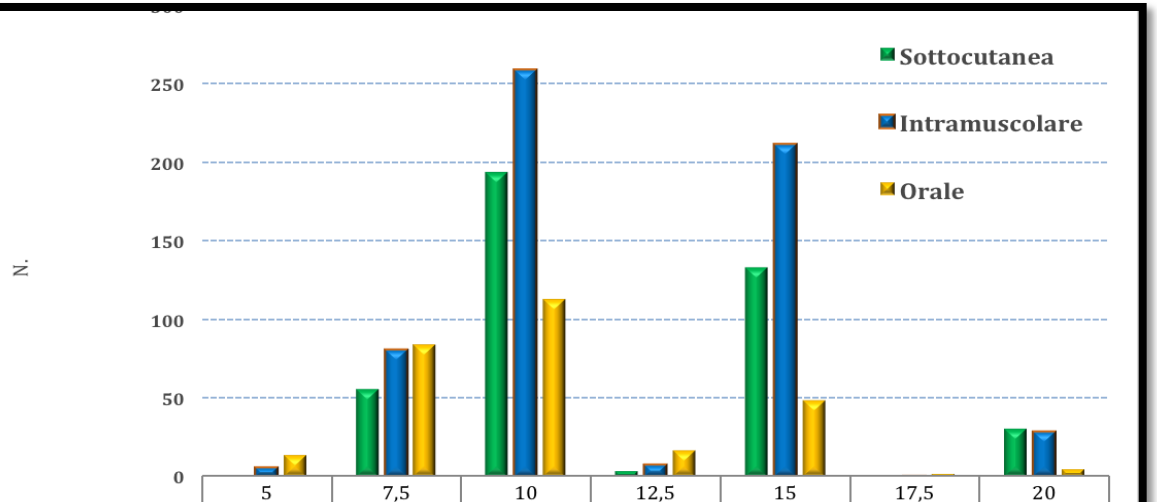
Half % patients in both groups were taking low-medium MTX dosage.

	p-value
Mean initial v	0.002 [0.000]°
Initial dose o	
5 mg	
7.5 mg	
10–12.5 mg	0.000
15 mg	
≥20 mg	



3) INITIAL FORMULATION

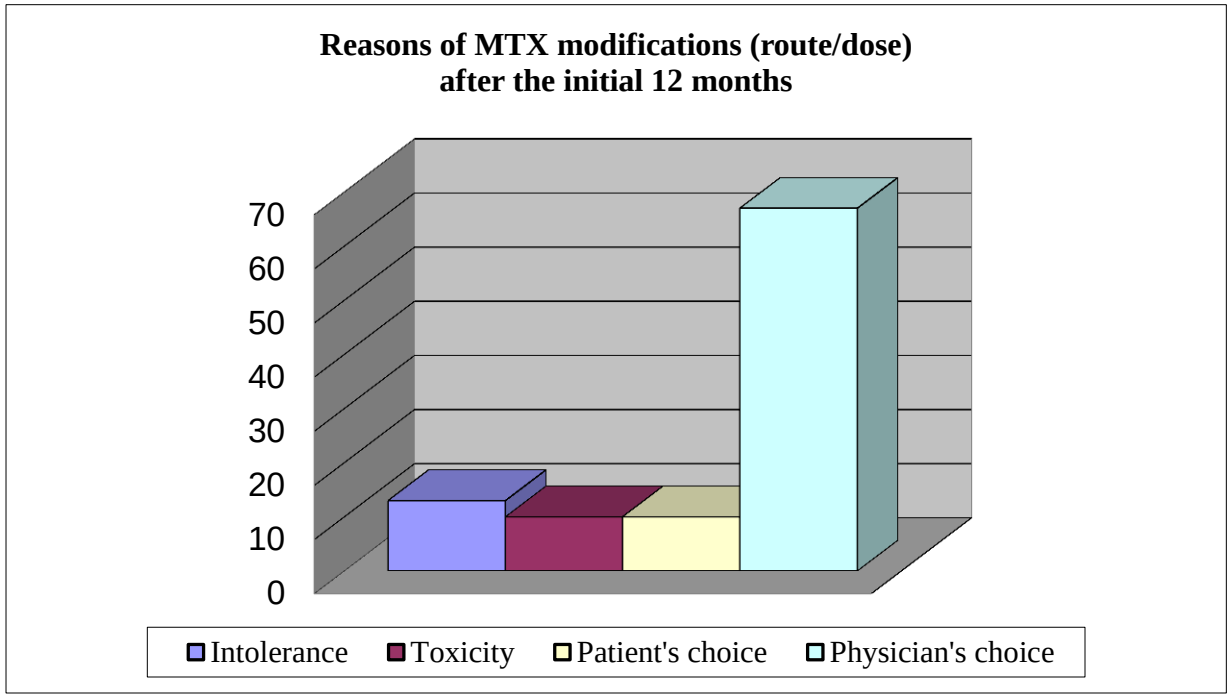
At the beginning the most preferred formulation was IM>SC>ORAL



	5	7,5	10	12,5	15	17,5	20
Sottocutanea	1	56	194	4	133	1	31
Intramuscolare	6	81	259	8	212	1	29
Orale	14	84	113	17	49	2	5

4) MODIFICATION OF INITIAL THERAPY (AFTER 12 MONTHS)

37% patients modified their initial MTX scheme after 12 months



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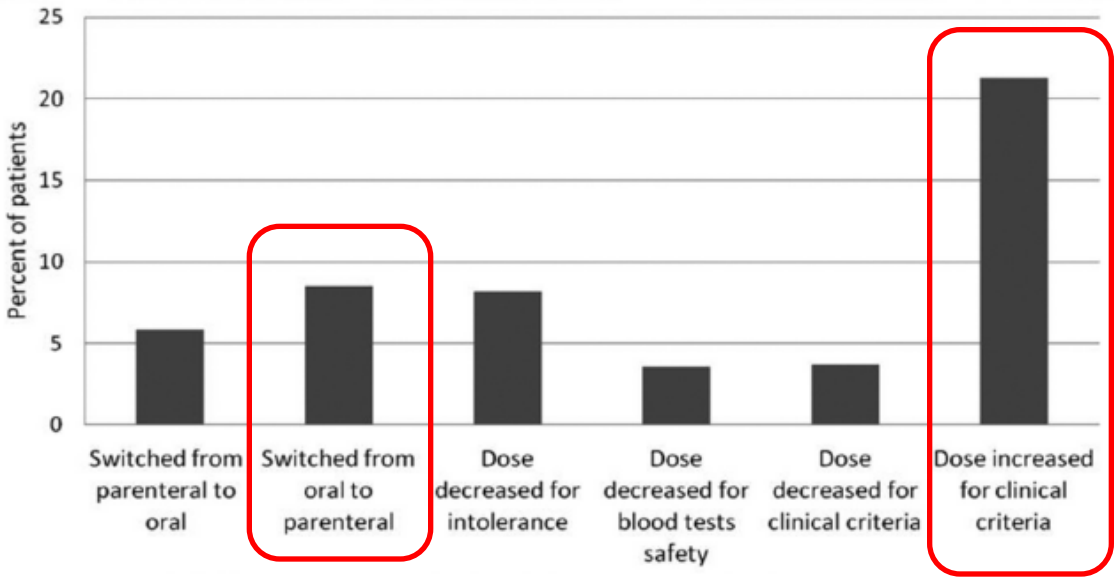

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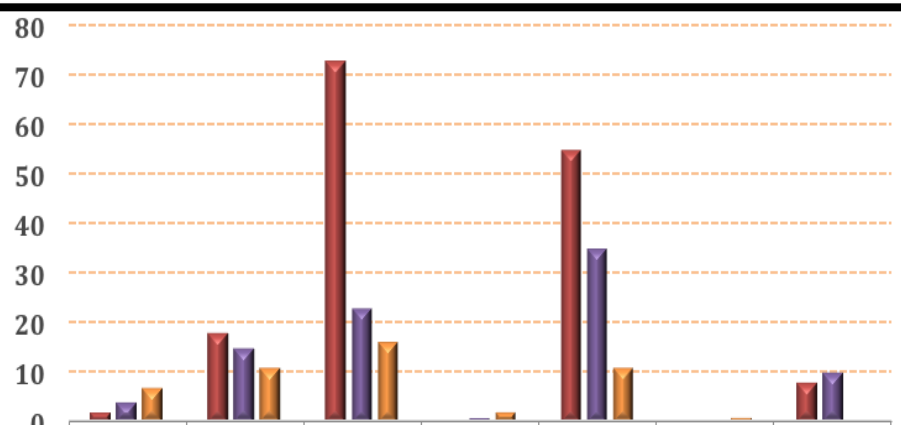

	5	7,5	10	12,5	15	17,5	20
Sottocutanea	2	18	73	0	55	0	8
Intramuscolare	4	15	23	1	35	0	10
Orale	7	11	16	2	11	1	0

At MTX modification, the most frequently adopted route of administration was the SC (54,2%), followed by IM (29,4%) and oral (16,4%) ones.

CURRENT MODALITIES OF MTX PRESCRIPTIONS: DOSAGE

Current mean dose was significantly higher in the parenteral group.

Half patients were on low-medium MTX dosage.

	Oral	Parenteral	*p*-value
M			
C			
5			
7			
1			
1			
12.5 – 15 mg	[illegible]	[illegible]	
≥15 mg	5.2%	8.2%	

DAS28 remission was observed in 58.5% of the patients.

52.9% of the patients who were not on remission received suboptimal MTX doses (<15 mg/week).

Suboptimal methotrexate use in rheumatoid arthritis patients in Italy: the MARI study

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Clinical and Experimental Rheumatology 2015; **33**: 895-899.

- The results of this study indicate that the **weekly MTX dose for the treatment of RA is often suboptimal, despite inadequate control of the disease activity.**

- **Continuous adjustments** of the dose are commonly required in routine clinical practice, even for patients who have been on treatment for a long time.

Adherence to current recommendations on the use of Methotrexate in Rheumatoid Arthritis in Italy: results from the MARI study

M. Manara[1], G. Bianchi[2], E. Bruschi[3], V. Azzolini[4], N. Belai Beyene [5], S. Corbanese[6], F. De Gennaro[7], L.S. Martin-Martin[8], A.B. Molica[9], M.R. Pozzi[10], N. Romeo[11], T. Rossini[12], A. Severino[13], L. Sinigaglia[1]

Clinical and Experimental Rheumatology 2016; **34**: 000-000.

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Reumatismo, 2013; 65 (5): 207-218

Systematic review of 2008-2012 literature and update of recommendations for the use of methotrexate in rheumatic diseases, with a focus on rheumatoid arthritis

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[1]Rheumatology, IRCCS S. Matteo, University of Pavia; [2]Rheumatology, Istituto Ortopedico G. Pini, Milan; [3]Rheumatology, University of Genoa; [4]Rheumatology, University of Ferrara; [5]Rheumatology, University of Modena and Reggio Emilia; [6]Rheumatology, University of Pisa, Italy

Table I. Proportion of patients with rheumatoid arthritis on methotrexate treatment satisfying audit criteria derived from Italian recommendations. Values are given as number of subjects fulfilling the criteria/ number of subjects assessed (percentages).

Theme of care	Recommendation	Criteria	Attainment
Preliminary tests	The work-up for RA patients who are MTX candidates should include the following tests: liver function tests; serum albumin; blood cell counts; serum creatinine.	Patients with lab tests performed before starting MTX	1252/1336 (93.7%)
	The work-up for RA patients who are MTX candidates should include the following tests: … hepatitis B and C serology.	Patients with hepatitis B and C serology performed before starting MTX	861/1336 (64.4%)
	The work-up for RA patients who are MTX candidates should include … chest x-ray.	Patients with x-ray performed before starting MTX	767/1336 (57.4%)
	MTX treatment should not be introduced during pregnancy	Female patients potentially pregnant with pregnancy test performed before starting MTX	42 /385 (10.9%)
MTX dosage	The therapeutic range of MTX is 7.5-25 mg/week.	Patients with current MTX dosage between 7.5-25 mg/week	1283 /1314 (97.6%)
	The optimal initial strategy is a starting dose of 12.5-15 mg/week.	Patients with starting MTX dosage between 12.5-15 mg/week	298 /1044 (28.5%)
	As MTX-related toxicity is dose-dependent, the maximum weekly dose of 25 mg should not be exceeded.	Patients with current MTX dosage under 25 mg/week	1313 /1314 (99.9%)
Folic acid supplementation	Weekly supplementation with folic acid ... should be administered to reduce the risk of adverse events/intolerance	Patients supplemented with folic / folinic acid	1282/1336 (96%)
	Weekly supplementation with folic acid (5-10 mg/week) should be administered ...	Patients supplemented with folic acid at a dosage between 5-10 mg/week	789/869 (90.8%)
Monitoring	Transaminases (AST, ALT) are the most useful laboratory parameters for monitoring liver toxicity due to MTX. CBC and renal function tests should also be performed in patients receiving MTX. These tests should be performed … every 4-12 weeks to check for hepatic, haematological or renal toxicity.	Patients with lab tests performed every 4-12 weeks	1179 /1314 (89.7%)

RA: rheumatoid arthritis; MTX: methotrexate.

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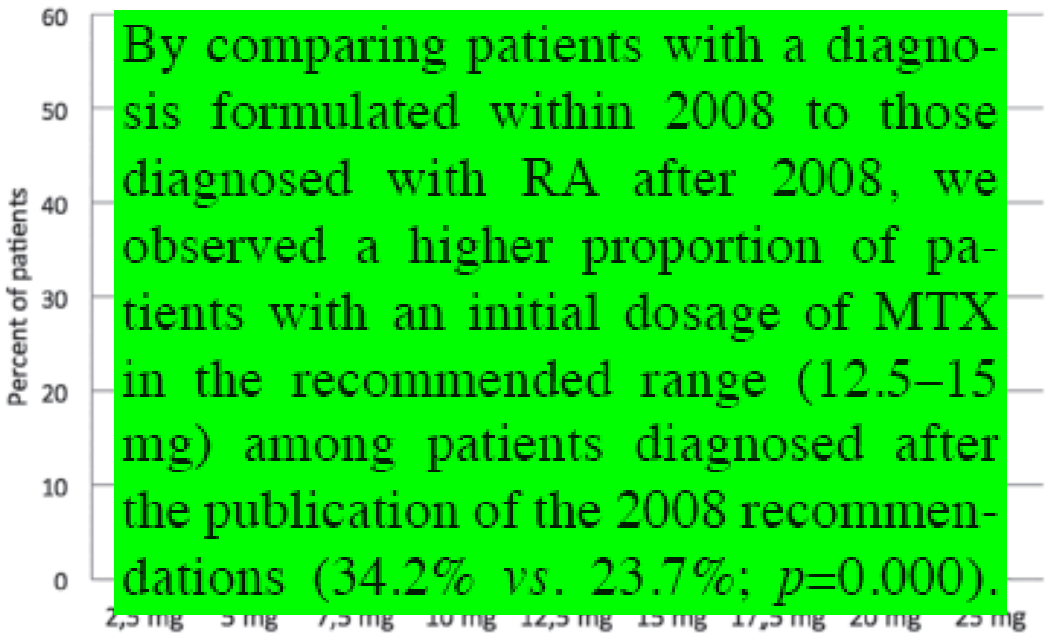
Fig. 1. Proportion of patients according to initial dose of MTX.



By comparing patients with a diagnosis formulated within 2008 to those diagnosed with RA after 2008, we observed a higher proportion of patients with an initial dosage of MTX in the recommended range (12.5–15 mg) among patients diagnosed after the publication of the 2008 recommendations (34.2% *vs.* 23.7%; p=0.000).

Ann Rheum Dis 2009;**68**:1086–1093.

Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative

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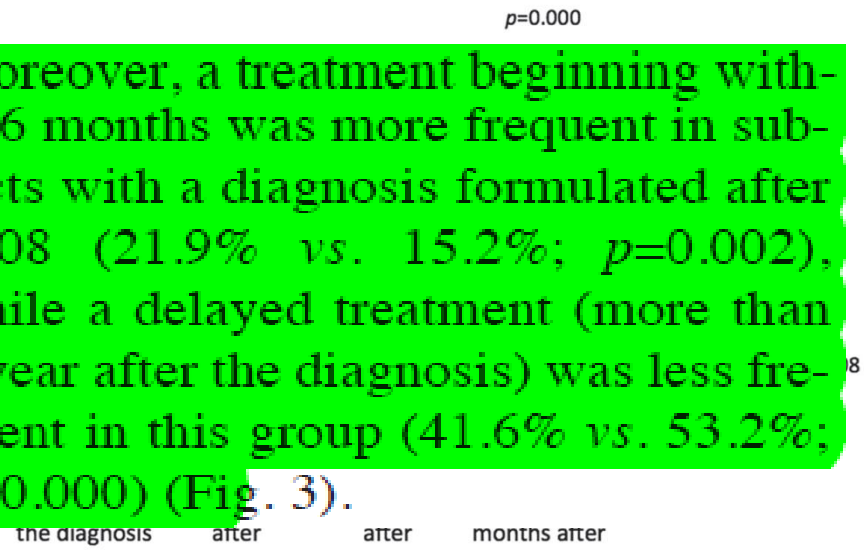
Fig. 3. Proportion of patients according to the time of starting MTX after the diagnosis.



Moreover, a treatment beginning within 6 months was more frequent in subjects with a diagnosis formulated after 2008 (21.9% *vs.* 15.2%; p=0.002), while a delayed treatment (more than 1 year after the diagnosis) was less frequent in this group (41.6% *vs.* 53.2%; p=0.000) (Fig. 3).

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Reumatismo, 2010; 62(1):34-45

LAVORO ORIGINALE

Consensus italiana* sulle raccomandazioni per l'utilizzo del methotrexate nelle malattie reumatiche con focus sull'artrite reumatoide: i risultati della "3E initiative"

Italian consensus on the recommendations about the use of methotrexate for the treatment of rheumatic diseases with a focus on rheumatoid arthritis: results from the "3E initiative"

F. De Leonardis[1], S. Alivernini[2], E. Bonacci[3], A.M. Buono[4], S. Bombardieri[5], G.F. Ferraccioli[2], C. Montecucco[3], L. Sinigaglia[6], F. Trotta[1], G. Valentini[4]

[1]Reumatologia, Università di Ferrara; [2]Scuola di Specializzazione in Reumatologia dell'Università Cattolica del Sacro Cuore-Roma; [3]Reumatologia, Università di Pavia; [4]Reumatologia, Seconda Università di Napoli; [5]Reumatologia, Università di Pisa; [6]U.O. di Reumatologia DH, Ospedale G. Pini, Milano

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Have we learned the lessons?!

THE EARLIER, THE BETTER

THE HIGHER, THE BETTER

THE SC, THE BETTER

BUT…WE STILL COULD DO BETTER….!

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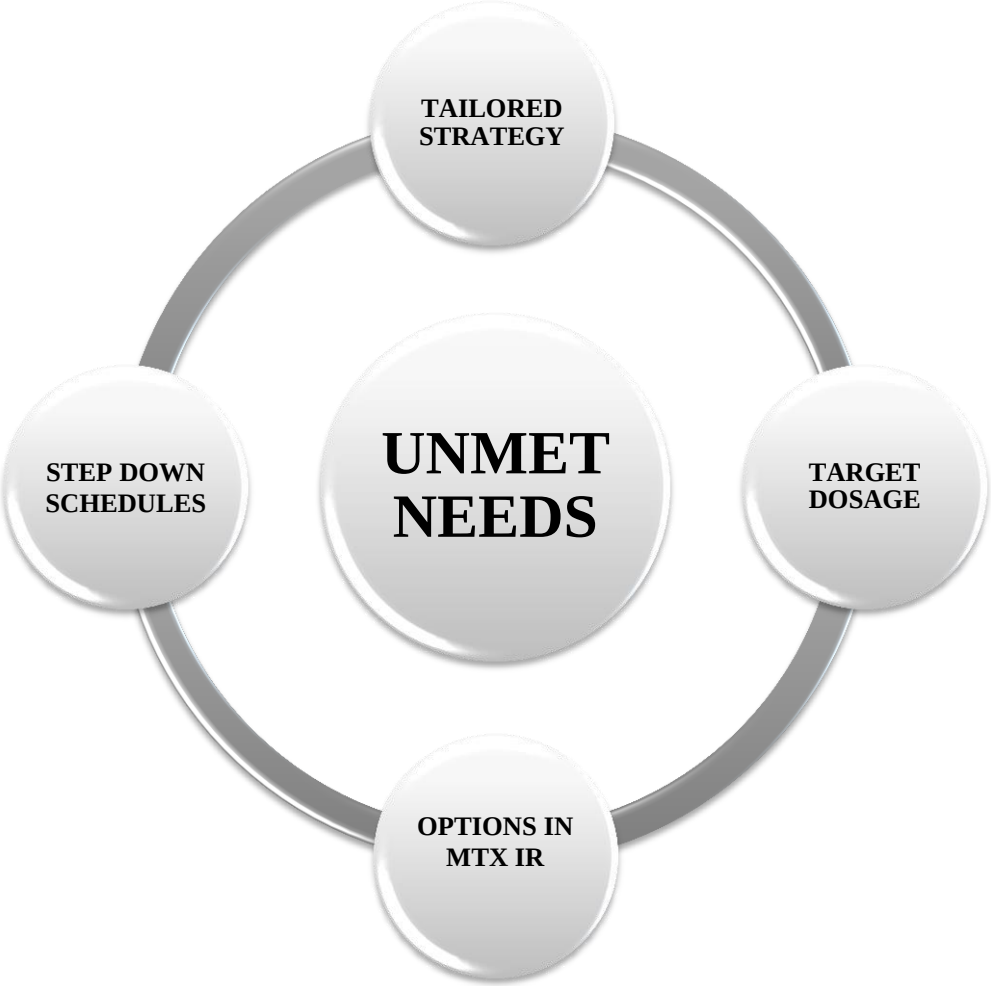
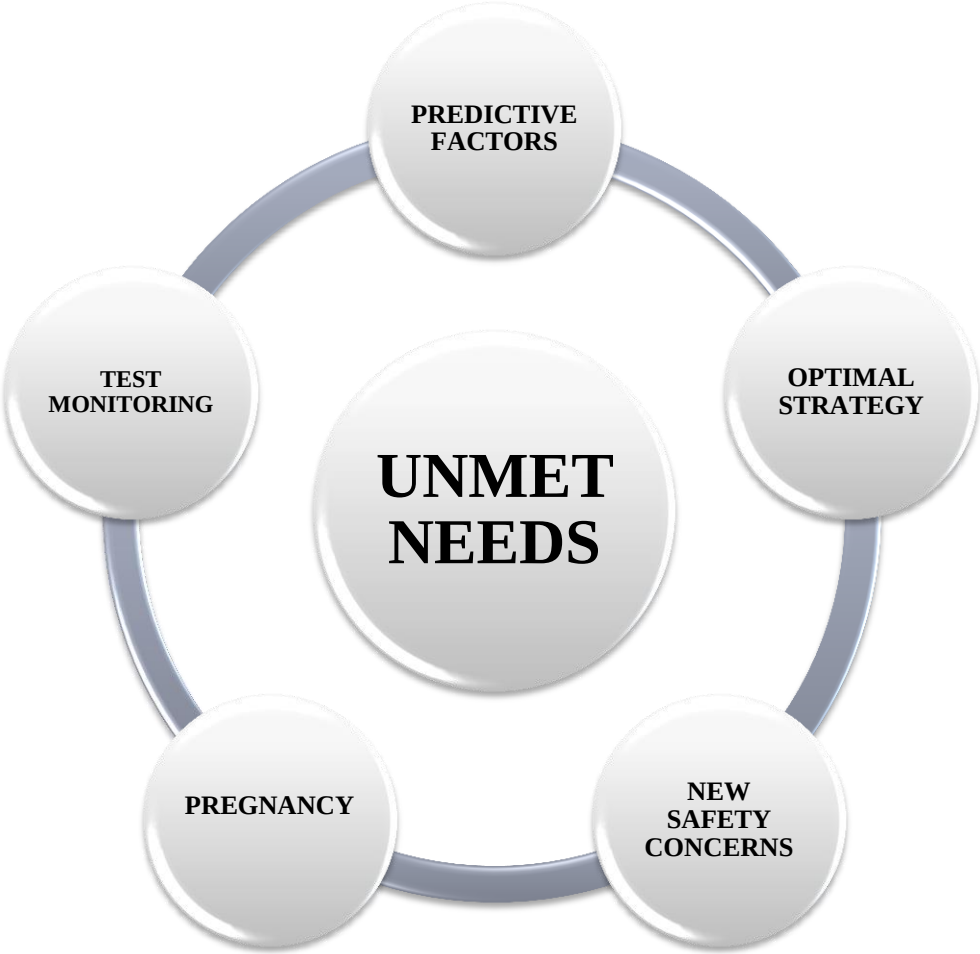
MTX EFFICACY UNMET NEEDS



MTX SAFETY: UNMET NEEDS



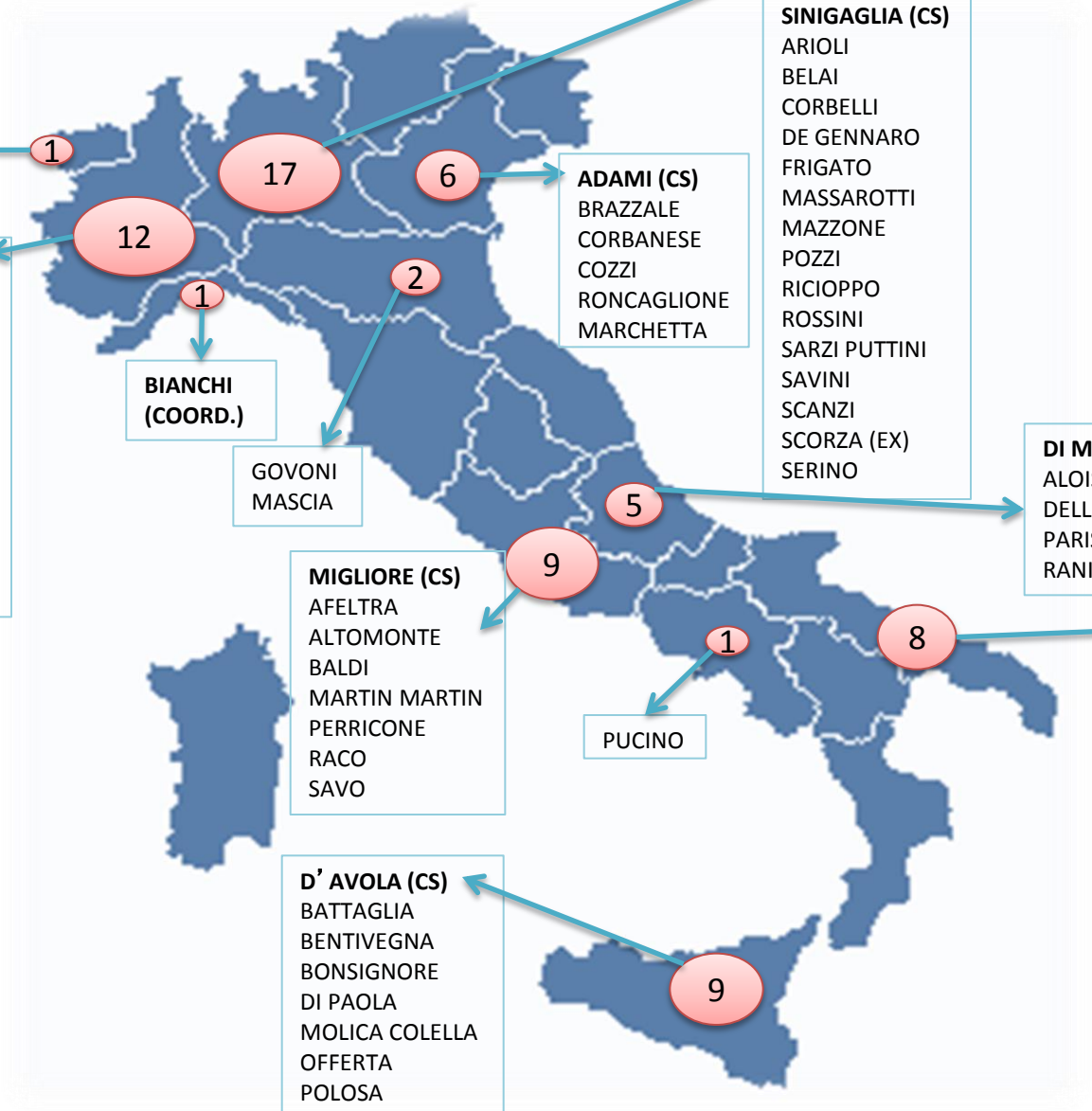
MTX: UNMET NEEDS

CLINICAL TRIALS/CTs

REAL LIFE DATA

GOOD LUCK!

THANKS



BELFIORE

AGNES
AZZOLINI
BIGO
CAVALLARO
FUSARO
PELLERITO
PICCOLO
ROMEO
SAINAGHI
SCARFO'
TRABALLI
VERDONE

BIANCHI (COORD.)

GOVONI
MASCIA

EPIS (CS)
SINIGAGLIA (CS)
ARIOLI
BELAI
CORBELLI
DE GENNARO
FRIGATO
MASSAROTTI
MAZZONE
POZZI
RICIOPPO
ROSSINI
SARZI PUTTINI
SAVINI
SCANZI
SCORZA (EX)
SERINO

ADAMI (CS)
BRAZZALE
CORBANESE
COZZI
RONCAGLIONE
MARCHETTA

DI MATTEO (CS)
ALOISANTONIO
DELLE MONACHE
PARISI
RANIERI

MIGLIORE (CS)
AFELTRA
ALTOMONTE
BALDI
MARTIN MARTIN
PERRICONE
RACO
SAVO

PUCINO

MURATORE (CS)
BUCCI
CARLINO
COZZOLONGO
LAPADULA
MONNO
SEMERARO
ZUCCARO

D' AVOLA (CS)
BATTAGLIA
BENTIVEGNA
BONSIGNORE
DI PAOLA
MOLICA COLELLA
OFFERTA
POLOSA
PRICOCO