Μεθοτρεξάτη ενέσιμη: νεότερα δεδομένα

Αλέξιος Ηλιόπουλος

Ρευματολογικό Τμήμα ΝΙΜΤΣ

Σύγκρουση συμφερόντων
Conflict of interest

Παρουσίαση με χορηγία φαρμακευτικής εταιρείας

Εκπαιδευτικές-ερευνητικές-συμβουλευτικές επιχορηγήσεις την τελευταία 5ετία:

Amgen-GSK, BMS, UCB, MSD, Pfizer, Novartis, Enorasis, Abbvie, Lilly

Περίγραμμα της παρουσίασης

Νεότερα στην MTX:

- Νεότερα δεδομένα στον μηχανισμό δράσης και την φαρμακοκινητική της MTX
- Υποδόρια και από του στόματος χορήγηση
  - Υπάρχει διαφορά στην αποτελεσματικότητα;
  - Υπάρχει διαφορά στην ασφάλεια;
- Οδηγίες και συμπεράσματα

«Μπορεί να ειπωθεί ειλικρινά, ότι η χρήση της MTX στην θεραπεία της PA έχει αλλάξει την ρευματολογία σαν ειδικότητα, και έχει υψώσει τις θεραπευτικές προσδοκίες για τους ασθενείς και για τις φαρμακευτικές εταιρίες να αναπτύξουν νέα φάρμακα, υψώνοντας τον πήχη για την έγκριση νέων φαρμάκων»

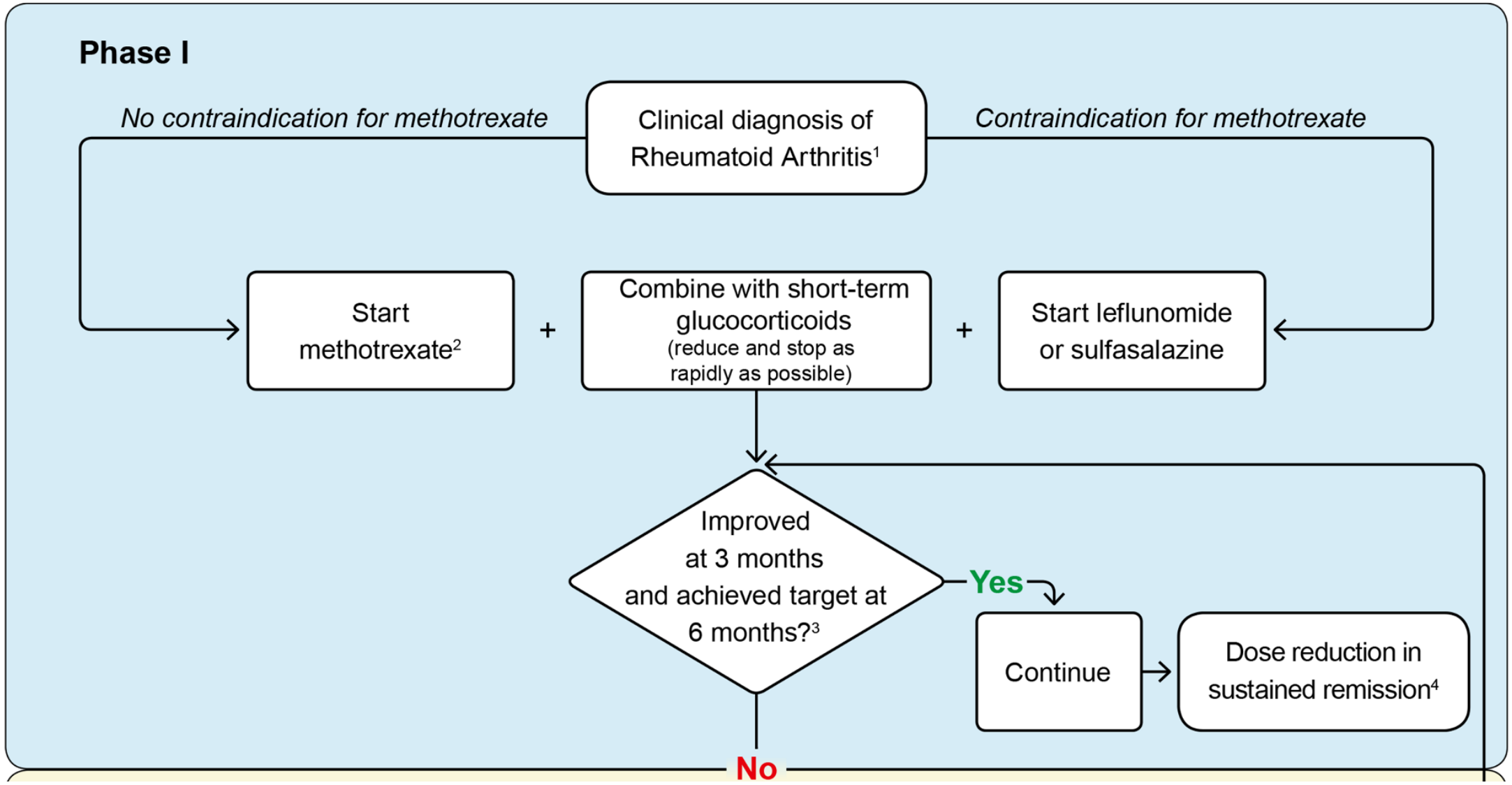
OLD DRUGS CAN LEARN NEW TRICKS

METHOTREXATE AND ITS MECHANISM OF ACTION

BY BRUCE N. CRONSTEIN, MD

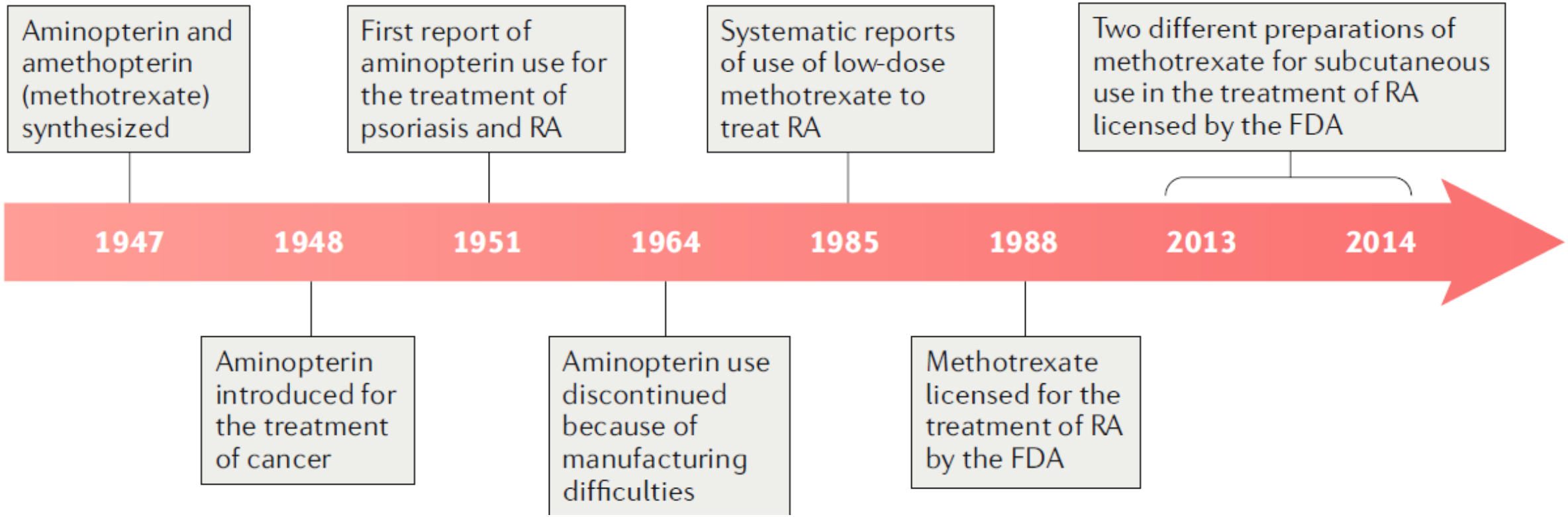
RHEUMATOLOGIST 2011

Οι τελευταίες οδηγίες της EULAR για την θεραπεία της PA

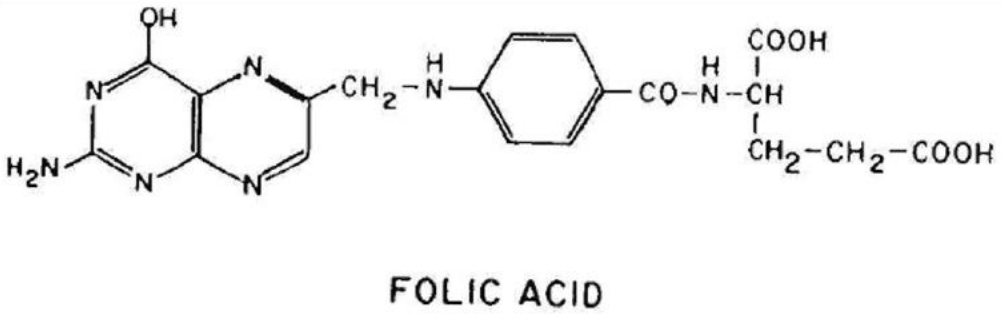


Smolen JS, Ann Rheum Dis 2023;82:3–18

Η ανάπτυξη της MTX



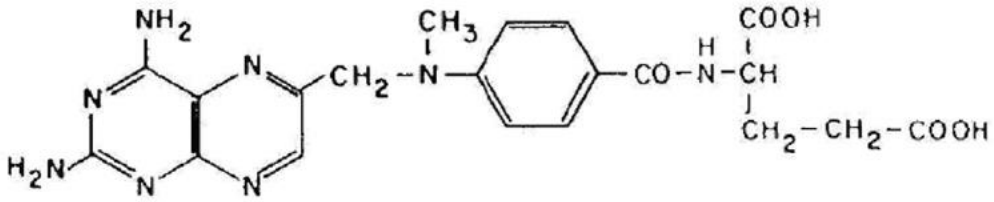
Cronstein BN, Aune TM. Nat Rev Rheumatol. 2020;16(3):145-154



FOLIC ACID

Fig. 1. Structures of folic acid, folinic acid, and methotrexate

Η MTX σχεδιάστηκε το 1940 σαν παρόμοιο ανάλογο του φολικού οξέος, ώστε να μπλοκάρει τα εξαρτώμενα από το φολικό οξύ σκαλοπάτια στην de novo βιοσύνθεση των πουρινών και πυριμιδινών στην θεραπεία του καρκίνου



METHOTREXATE

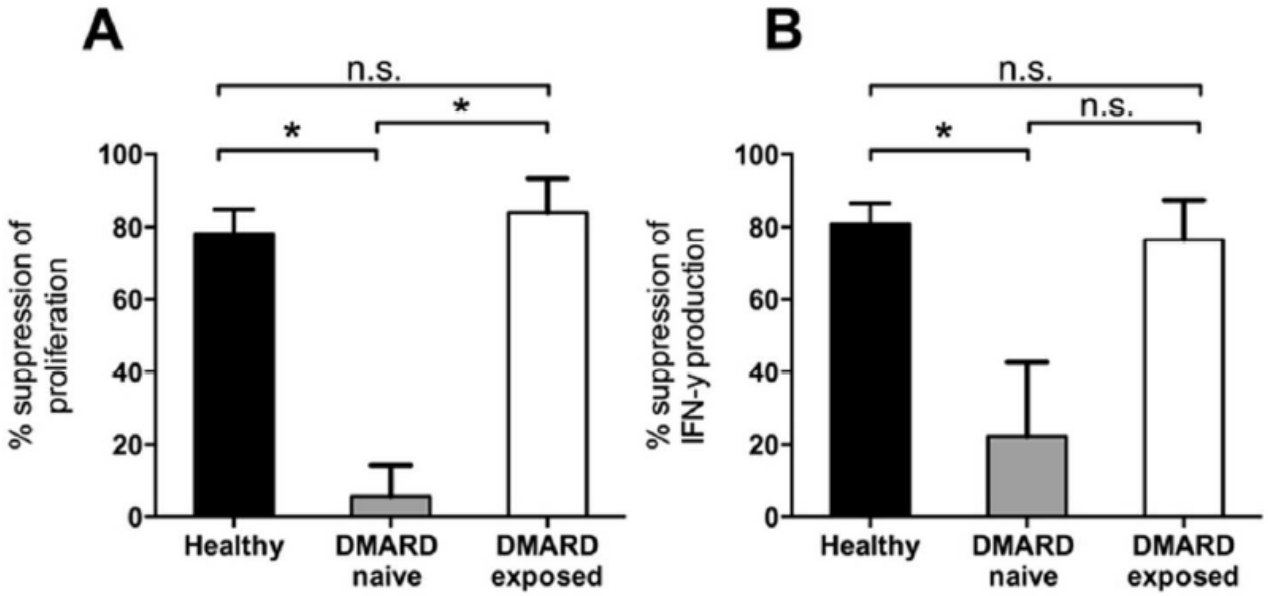
Η MTX είναι ανταγωνιστής του φολικού οξέος

- **Η συγχορήγηση ΦΟ έχει σαν αποτέλεσμα μείωση κατά 80% των βλεννοδερματικών και γαστρεντερικών ανεπιθύμητων ενεργειών της MTX**
- **Το όφελος στην αύξηση των ηπατικών ενζύμων είναι της τάξης του 35%**

SL Morgan and JE Baggott, Clin Exp Rheumatol 2010; 28 (Suppl. 61):S102-S109

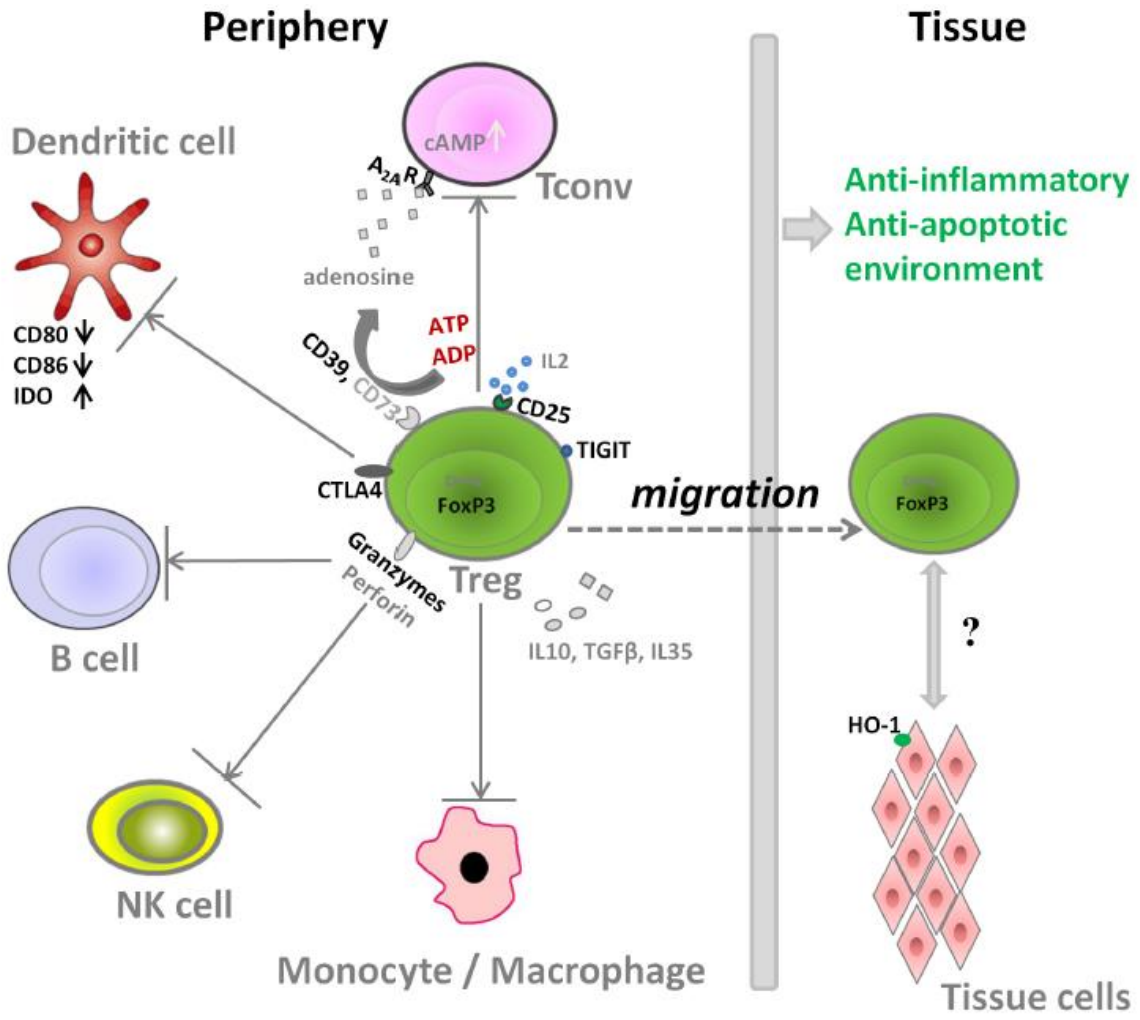
Η MTX επανορθώνει την λειτουργία των ρυθμιστικών Τ κυττάρων σε ασθενείς με PA

- Μειονεκτική λειτουργικότητα των Treg αναγνωρίζεται σε MTX-naïve ασθενείς με PA, ενώ σε ασθενείς υπό MTX έχει αποκατασταθεί η κατασταλτική λειτουργία των Tregs. Παράλληλα διαπιστώθηκε αυξημένη έκφραση Foxp3 και CTLA-4 στα Tregs.
- Νέος μηχανισμός δράσης της MTX είναι η αποκατάσταση της μειονεκτικής λειτουργίας των Treg μέσω απομεθυλίωσης του FOXP3 locus που οδηγεί σε επακόλουθη αύξηση στην έκφραση Foxp3 και CTLA-4



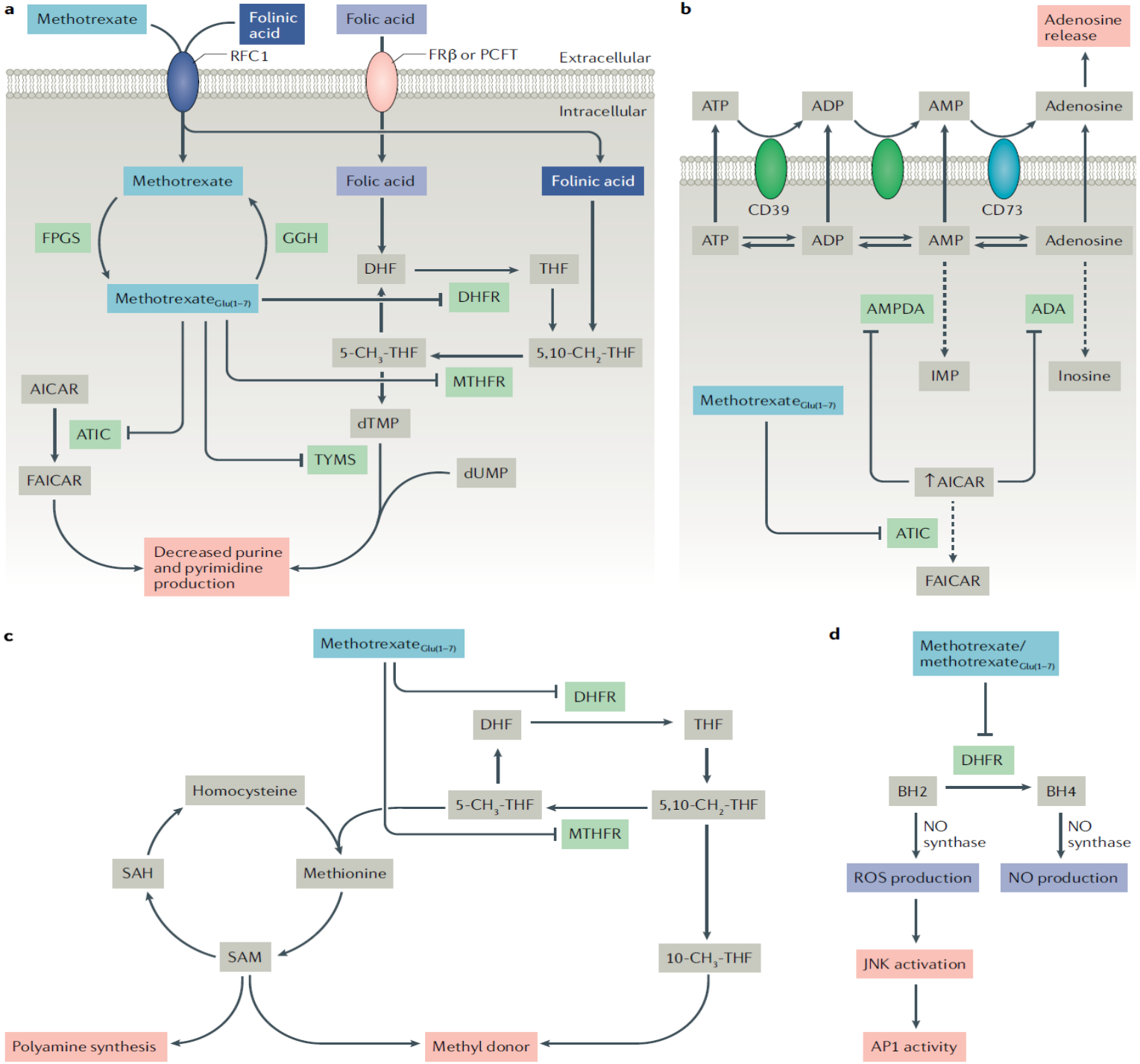
Cribbs AP, Arthritis Rheumatol. 2015;67:1182-92

Περιορισμός της φλεγμονής: Ο ρόλος των Tregs



- Τα ρυθμιστικά Τ κύτταρα που ευρίσκονται στους ιστούς έχουν δυνατότητα να παρεμβαίνουν και να καταστέλλουν την δραστηριότητα των κυττάρων του ανοσολογικού συστήματος
- Αναστέλλουν επίσης την λειτουργία των οστεοκλαστών, ενώ ενισχύουν την οστεοβλαστική σειρά από το επίπεδο του πολυδύναμου μεσεγχυματικού κυττάρου

Lei H, Front Pharmacol. 2015;6:184



Μηχανισμός δράσης της MTX

Cronstein BN, Aune TM. Nat Rev Rheumatol. 2020;16(3):145-154

Μηχανισμός δράσης της MTX

- Methotrexate polyglutamates inhibit aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase (ATIC), leading to intracellular accumulation of AICAR and increased adenosine release; adenosine binds to cell surface receptors and suppresses many inflammatory and immune reactions.
- Methotrexate inhibits dihydrofolate reductase, preventing the reduction of dihydrobiopterin (BH2) to tetrahydrobiopterin (BH4), leading to nitric oxide synthase uncoupling and increased sensitivity of T cells to apoptosis, thereby diminishing immune responses.
- Methotrexate inhibits activation of nuclear factor- κB (NF- κB) by increasing both adenosine release and activation of adenosine receptor A2a and by inhibiting the reduction of BH2 to BH4.
- Methotrexate increases the expression of long intergenic non- coding RNA p21 (lincRNA- p21), which is a multifunction long non- coding RNA that regulates, both directly and indirectly, a variety of critical immune and inflammatory processes.
- • By modulating cell- specific signalling pathways, methotrexate inhibits important pro-inflammatory properties of major cell lineages involved in rheumatoid arthritis pathogenesis, including T cells, macrophages, endothelial cells and fibroblast-like synoviocytes.

Cronstein BN, Aune TM. Nat Rev Rheumatol. 2020;16(3):145-154

Neutrophils

- Inhibits oxidant generation
- Inhibits adhesion and recruitment
- Inhibits neutrophil extracellular trap formation

Macrophages

- Increases M1 to M2 transformation
- Inhibits cytokine expression
- Inhibits osteoclast differentiation

T cells

- Inhibits T cell receptor-triggered activation
- Inhibits activation-induced cell death
- Inhibits FAS–FASL-mediated cell death
- Increases regulatory T (T_{reg}) cell differentiation
- Mediates T_{reg} cell-mediated suppression of T cell proliferation

Endothelial cells

- Increases barrier integrity
- Inhibits oedema formation

Fibroblast-like synoviocytes

- Inhibits metalloproteinase production

MTX: δράση μέσω απελευθέρωσης αδενοσίνης

In a randomized prospective study, ingestion of caffeine, a non- selective adenosine receptor antagonist, reduced the therapeutic response to methotrexate in patients with RA

Η καφεΐνη είναι ανταγωνιστής των υποδοχέων της αδενοσίνης, επομένως θα πρέπει να συστήνεται στους ασθενείς με ανεπαρκή απάντηση στην MTX να διακόπτουν την καφεΐνη για αρκετές εβδομάδες πριν αλλάξουν θεραπεία

Cronstein BN, Nat Rev Rheumatol 2020;16(3):145-154

Καφεΐνη επί δυσανεξίας σε MTX

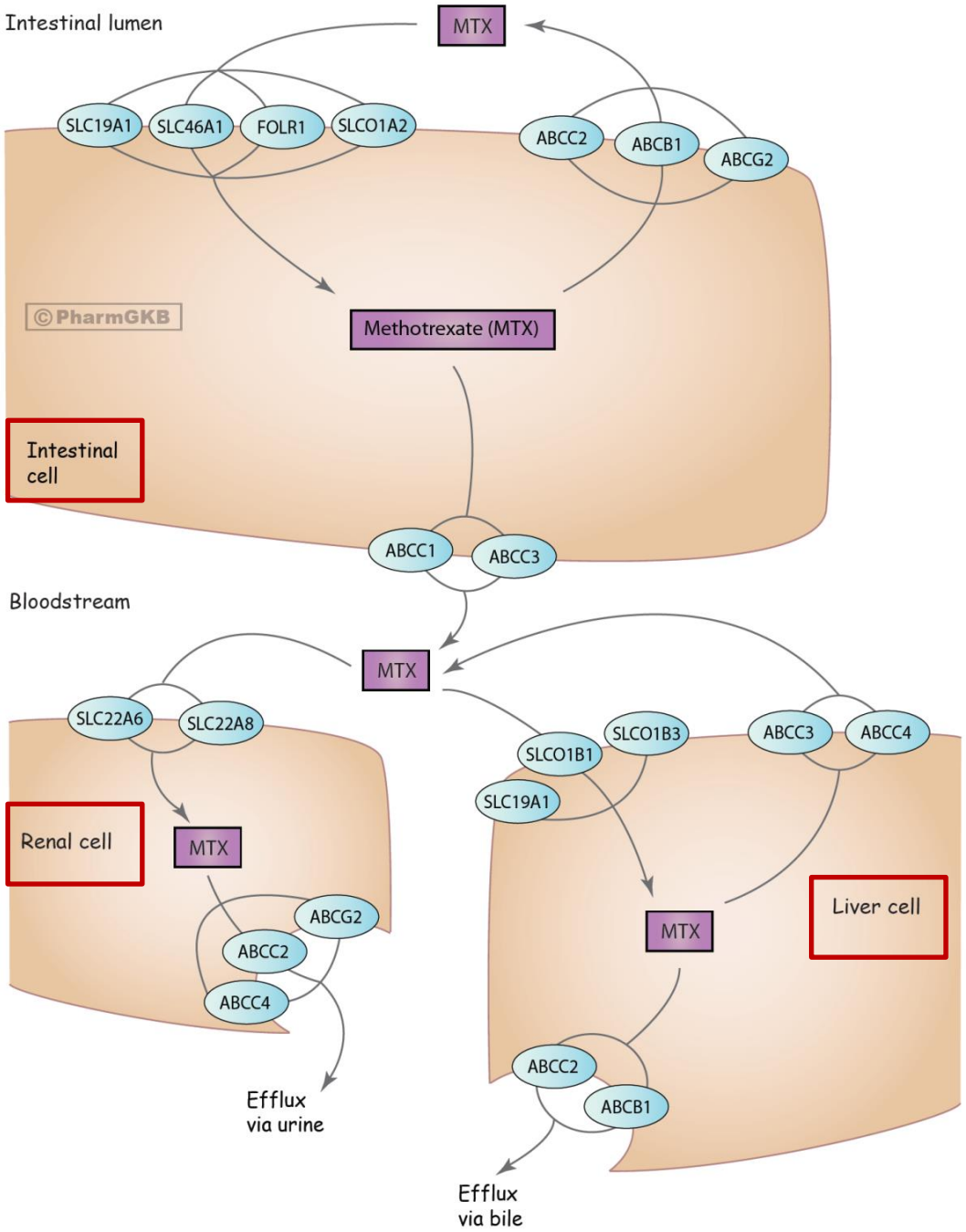
- Μία έως 1½ κουταλιά ‘instant coffee’ (containing ~30– 45 mg caffeine) σε 160 to 200 ml νερό (πρωί –βράδυ, επόμενο πρωί), συνολικά ~90 to 135 mg καφεΐνης σε 24 ώρες. Για όσους πίνουν ήδη καφέ, μερικά έξτρα φλυτζάνια
- Εναλλακτικά μαύρη σοκολάτα, 20 gr 1 ώρα πριν την λήψη MTX. Τα 20 g μαύρης σοκολάτας περιέχουν 22 mg caffeine, 14.8 mg theophylline and 424 mg of theobromine, όλα παράγωγα της μεθυλ-ξανθίνης.

Αποτελέσματα σε 120 ασθενείς με δυσανεξία:

- 66/120 (55 %) Complete relief—able to continue taking advised MTX dose
- 16/120 (13.3 %) Partial relief—able to continue taking advised MTX dose but only with antiemetics
- 9/120 (7.5 %) Minimal relief better but some symptoms persisting—able to continue taking reduced MTX dose and with antiemetics
- 12 (10 %) Caffeine failure—no relief at all.

Malaviya AN, Clin Rheumatol. 2017;36:279-285

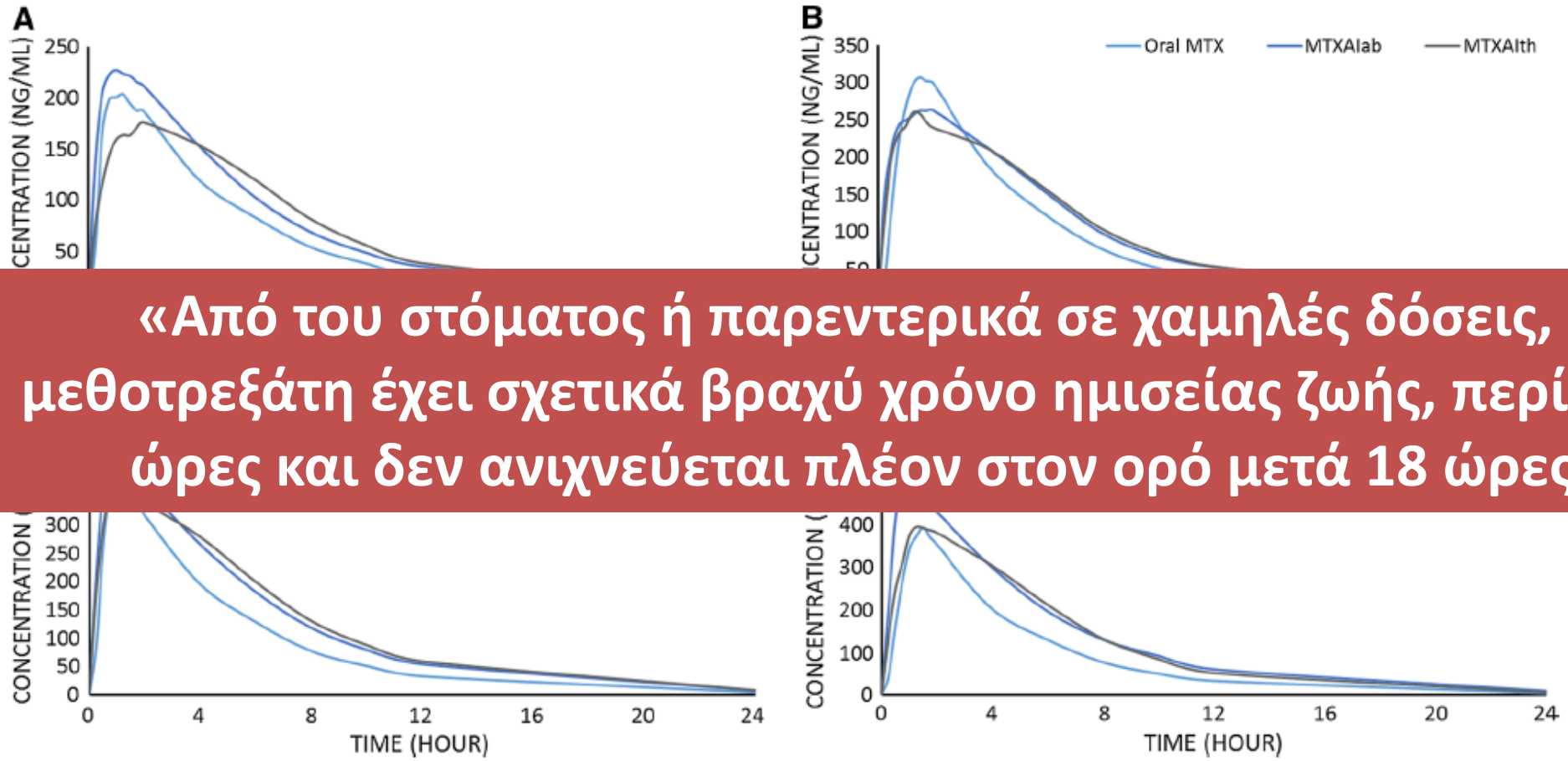
Νεότερα δεδομένα στον μεταβολισμό και την φαρμακοκινητική της ΜΤΧ -Υποδόρια και από του στόματος ΜΤΧ



Μονοπάτια μεταφοράς και φαρμακοκινητική της MTX

- **SLC19A1 solute carrier family 19 (folate transporter), member 1**
- **ABCC1 (ATP-binding cassette, subfamily C, member 1)**

MTX: Φαρμακοκινητική

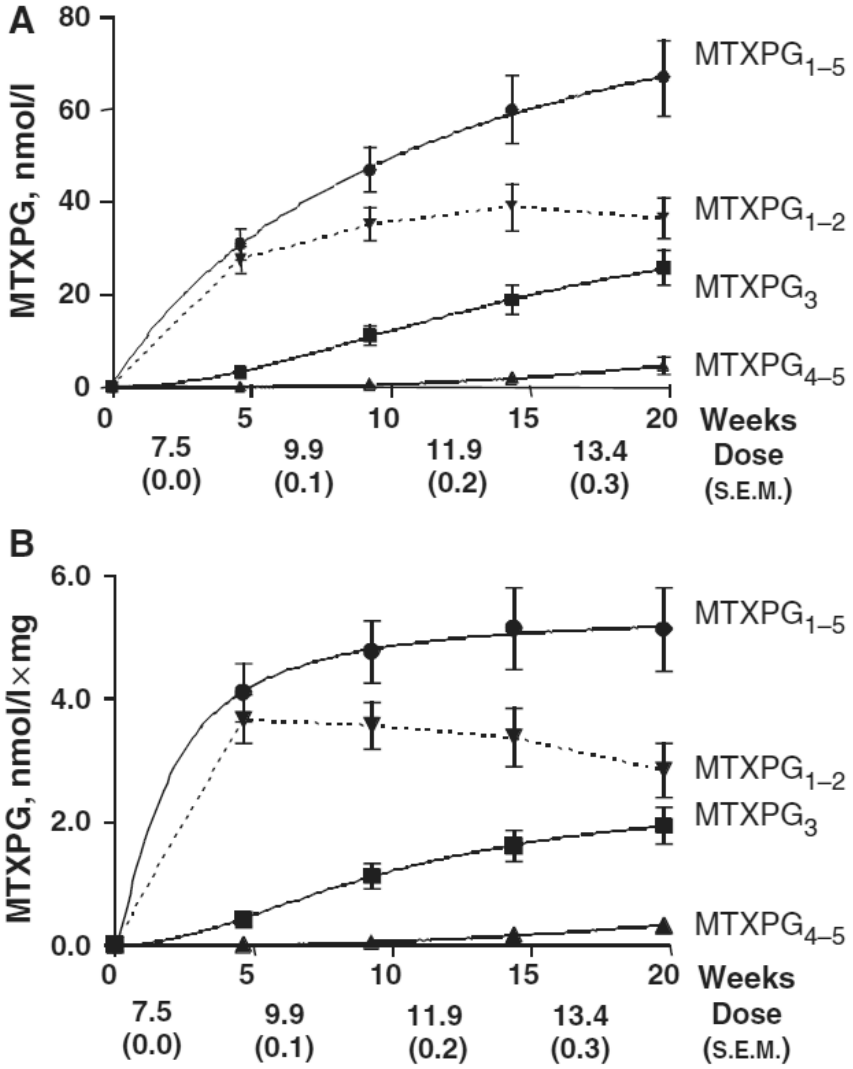


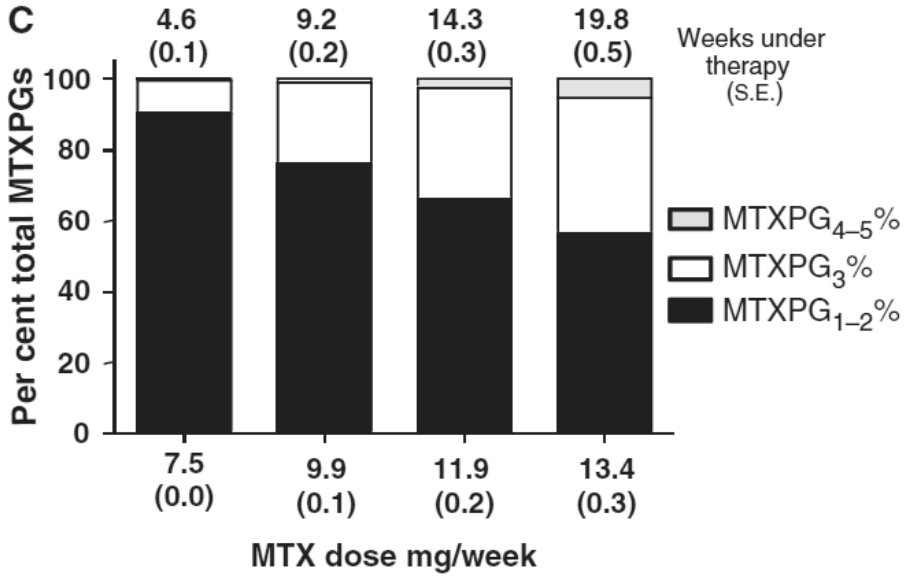
«Από του στόματος ή παρεντερικά σε χαμηλές δόσεις, η μεθοτρεξάτη έχει σχετικά βραχύ χρόνο ημισείας ζωής, περίπου 6 ώρες και δεν ανιχνεύεται πλέον στον ορό μετά 18 ώρες»

Συγκέντρωση MTX έναντι χρόνου από χορήγηση για oral MTX, MTX με ένεση στην κοιλιά και ένεση στο μηρό. a 10 mg dose, b 15 mg dose, c 20 mg dose, and d 25 mg dose

Schiff MH, Rheumatol Int 2017;37:213-218

Η MTX είναι προφάρμακο και η δράση της επιτελείται μέσω πολυγλουταμινικών κλασμάτων





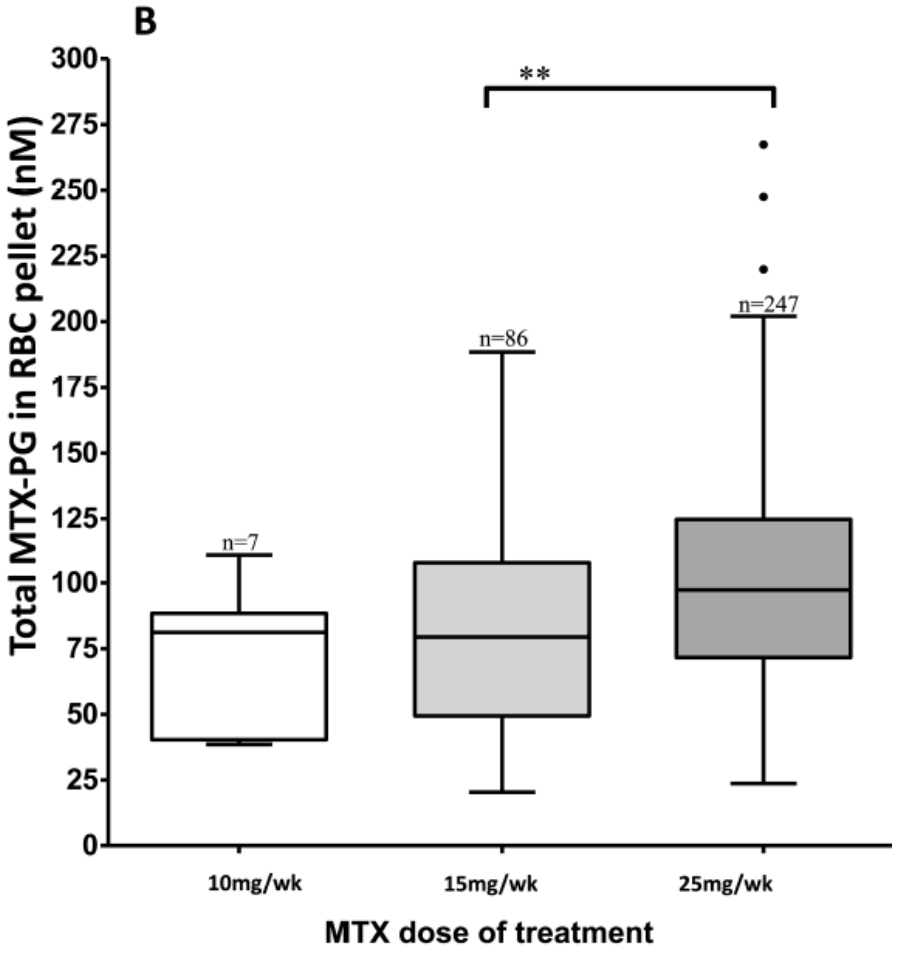
Ο σχηματισμός MTXPGs μακράς και πολύ μακράς αλύσου εξαρτάται από την δόση χορήγησης αλλά και από τον χρόνο έκθεσης

Dervieux T, Rheumatology 2010;49:2337–2345

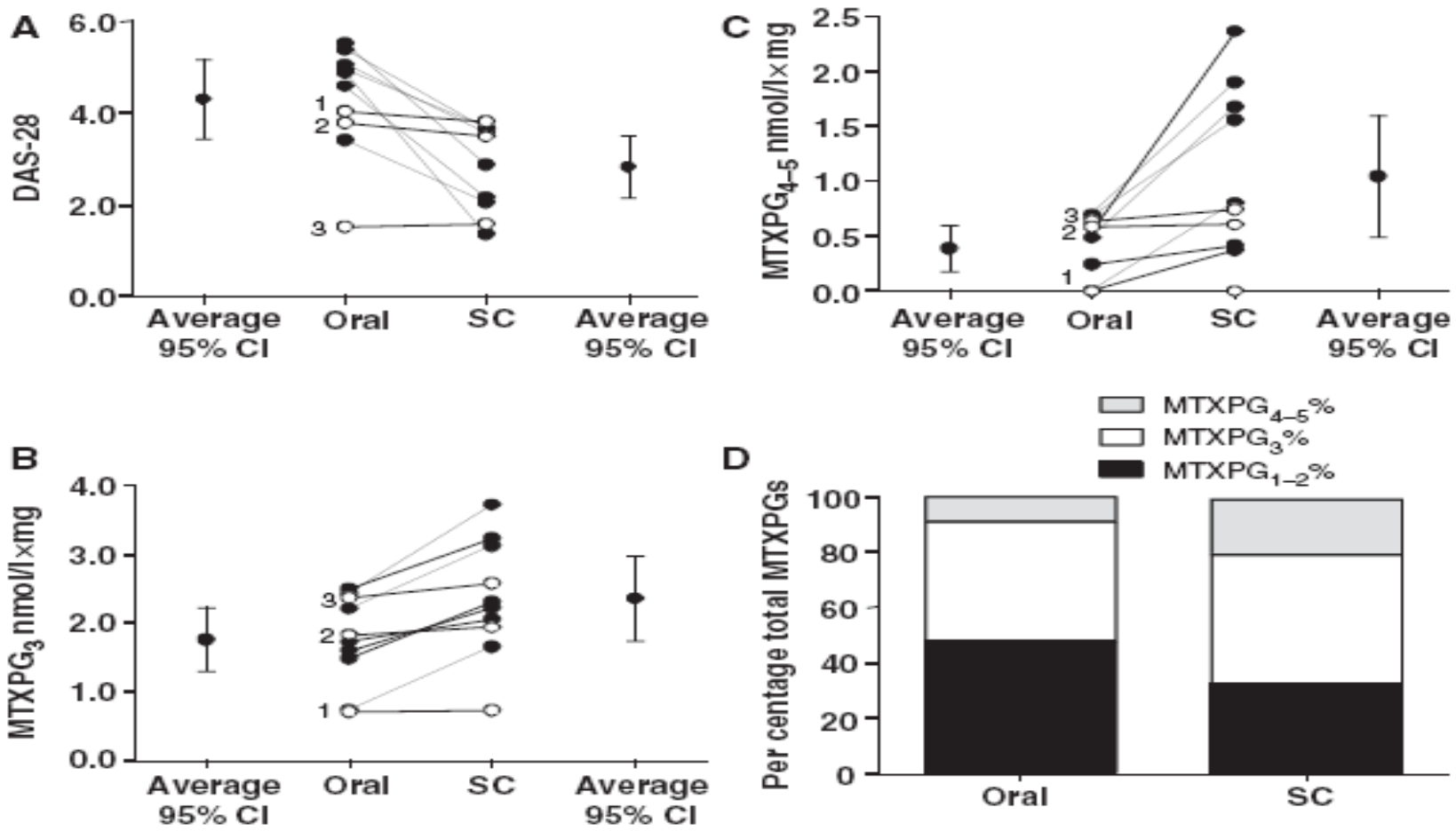
Determinants of Erythrocyte Methotrexate Polyglutamate Levels in Rheumatoid Arthritis

Ethan den Boer, Maurits C.J.F. de Rotte, Saskia M.F. Pluijm, Sandra G. Heil, Johanna M. Hazes, and Robert de Jonge

- **Η αποτελεσματικότητα της μεθοτρεξάτης έχει συσχετισθεί με την ενδοκυττάρια συσσώρευση των MTX-polyglutamate (MTX-PG)**
- **Σε Ολλανδική μελέτη με περίπου 350 ασθενείς μετρήθηκαν τα επίπεδα των MTX-PG, 3 μήνες μετά την έναρξη της αγωγής με MTX**
- **Θετικοί παράγοντες αύξησης των επιπέδων ήταν μεγαλύτερη ηλικία, μεγαλύτερη δόση, υψηλότερο επίπεδο φολικού στα ερυθροκύτταρα και ο τύπος του ενζύμου FPGS**



den Boer E, J Rheumatol 2014;41:2167–78

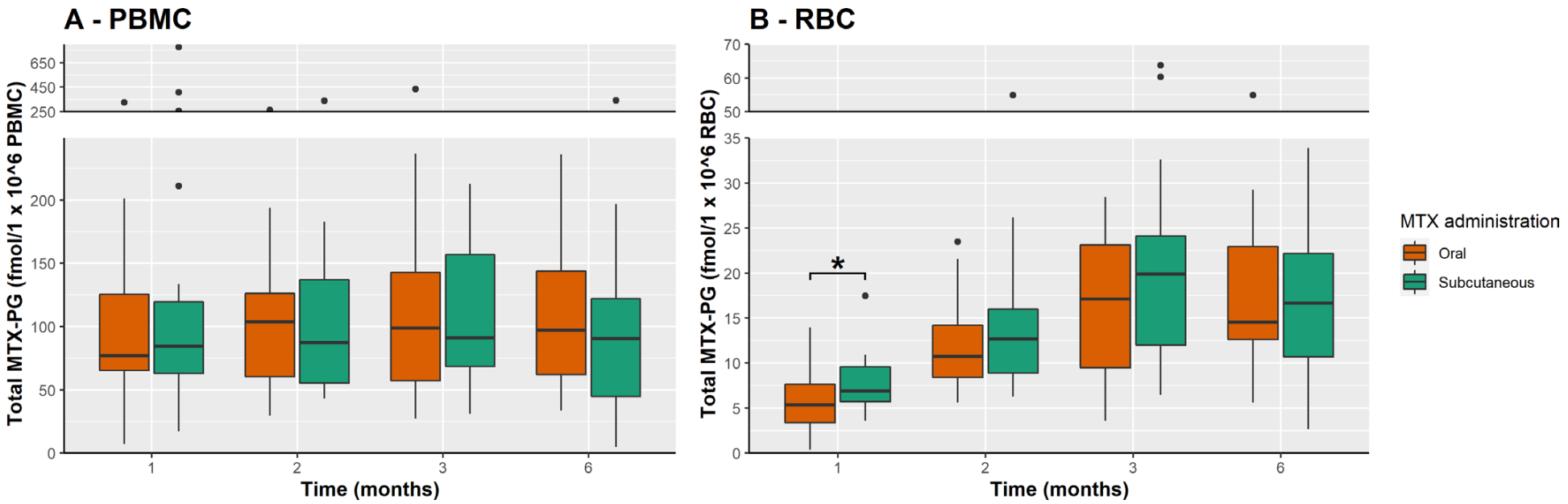


Αλλαγή από per os σε sc MTX

- Μείωση του DAS28 κατά 31%
- Αύξηση του ποσοστού MTXPG3 κατά 37%
- Αύξηση του ποσοστού MTXPG4-5 κατά 132%
- Η μείωση στο DAS28 σχετίζεται με την αύξηση του ποσοστού των MTXPG3 και MTXPG4-5

Dervieux T, Rheumatology 2010;49:2337–2345

Pharmacokinetics of oral and subcutaneous methotrexate in red and white blood cells in patients with early rheumatoid arthritis: the methotrexate monitoring trial

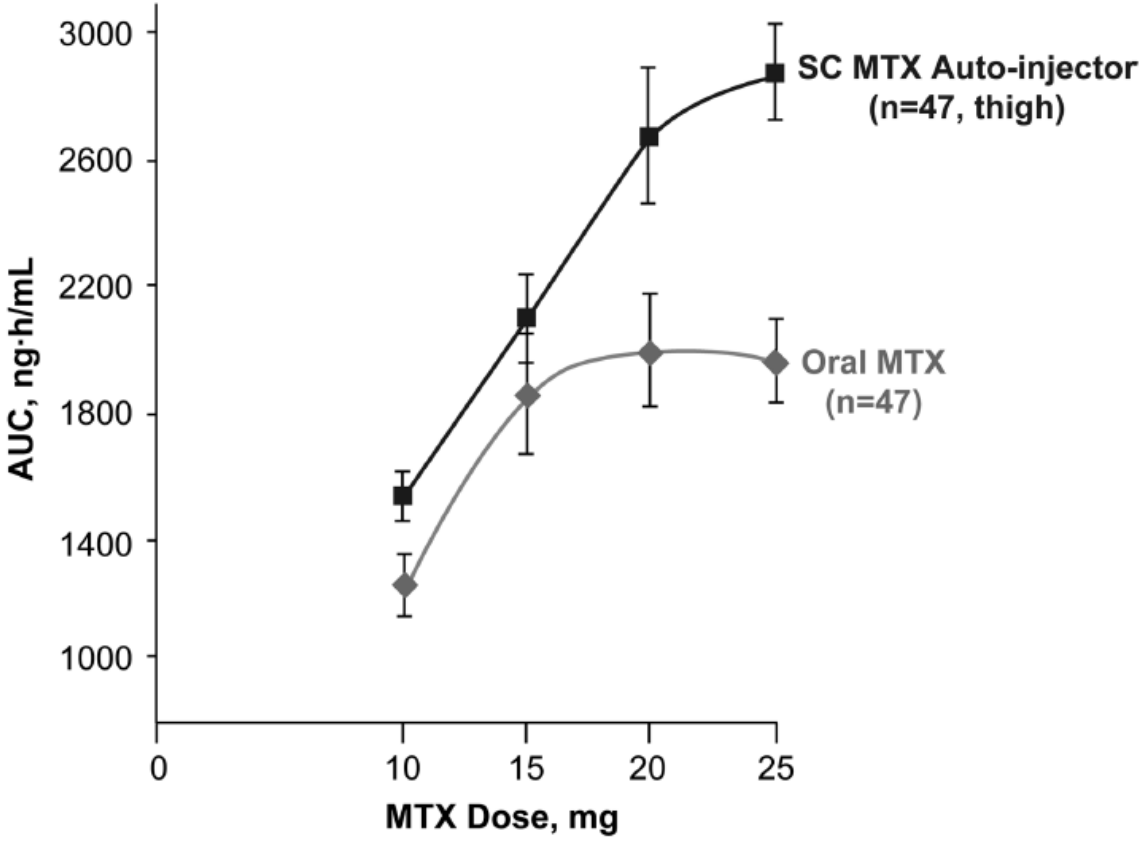


MTX-PG levels in PBMCs (panel A) and RBCs (panel B) after oral and subcutaneous use. *Indicates significant difference between oral and subcutaneous use (p=0.04) PBMC, peripheral blood mononuclear cell; PG, polyglutamate

Subcutaneous MTX administration results in higher drug levels in RBCs (but not in PBMCs) than after oral administration, especially shortly after treatment initiation.

Hebing RC, Ann Rheum Dis. 2023;82(4):460-467

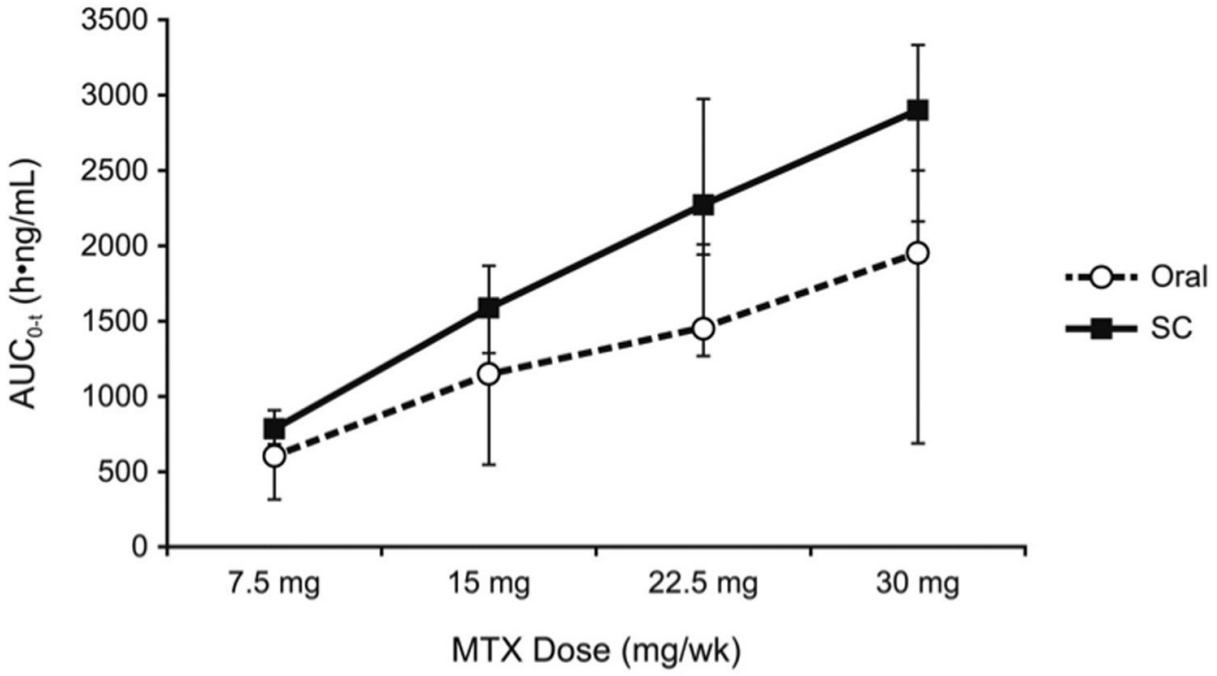
Βιοδιαθεσιμότητα υποδόριας και per os MTX



- **Η χορήγηση MTX σε δόση ≥15 mg/εβδομάδα από του στόματος φαίνεται να κάνει πλατό στην απορρόφηση**
- **Για ανεπαρκή θεραπευτική απάντηση σε δόσεις μικρότερες των 15mg/εβδομάδα προτείνεται η μετάβαση σε υποδόρια MTX**

Schiff MH, et al. Ann Rheum Dis 2014;73:1549–1551

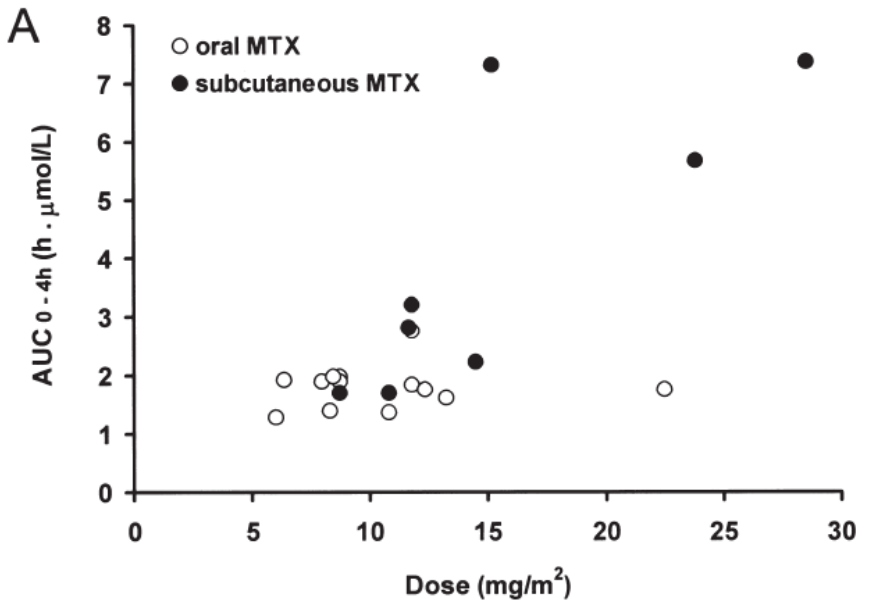
Βιοδιαθεσιμότητα υποδόριας και per os MTX

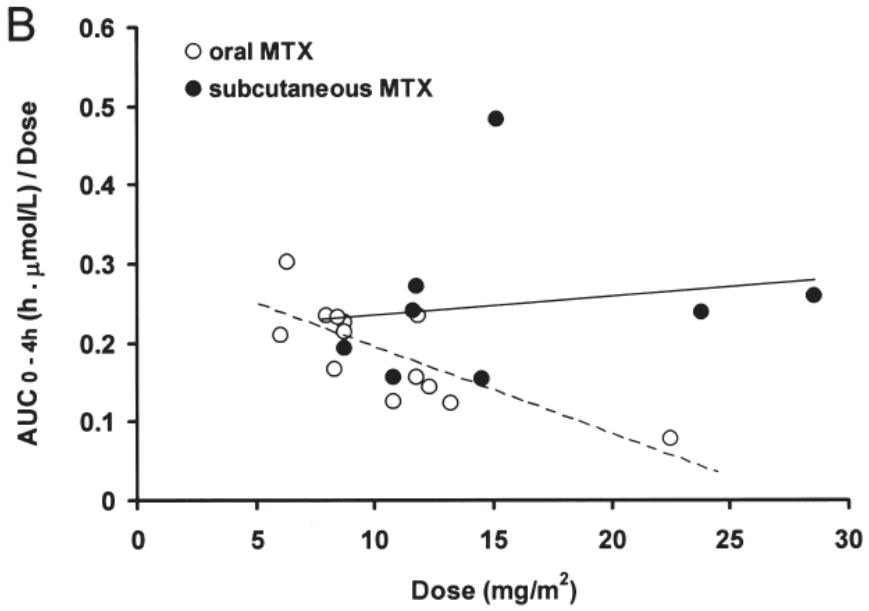


Median AUC_{0-t} of oral MTX and SC MTX pen at each dose evaluated

- **65 Υγιείς εθελοντές με κριτήρια αποκλεισμού:**
  - **>10 τσιγάρα ημερησίως**
  - **>5 φλυτζάνια καφέ ή άλλου ποτού που περιέχει ξανθίνη**
  - **Αυξημένη κατανάλωση αλκοόλ**
- **Προγεμισμένες πένες που περιέχουν 0.15, 0.3, 0.45, or 0.6 mL του 50-mg/mL MTX διαλύματος, αντιστοιχία με 7.5-, 15-, 22.5-, or 30-mg MTX tabl (2.5-mg per tablet)**

Pichlmeier U, Clin Exp Rheumatol 2014; 32: 563-571





Βιοδιαθεσιμότητα per os και sc MTX σε νεανική αρθρίτιδα

- Η per os χορήγηση είναι αποτελεσματική σε μικρές δόσεις MTX
- Σε χορήγηση υψηλοτέρων δόσεων παρουσιάζεται το φαινόμενο του κορεσμού στην εντερική απορρόφηση, επομένως η παρεντερική οδός είναι απαραίτητη όταν απαιτούνται υψηλότερες δόσεις

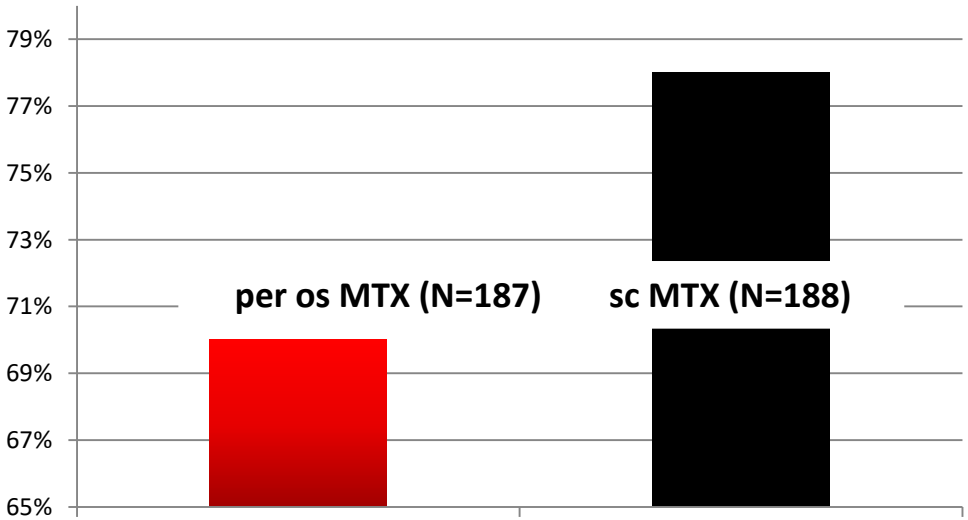
Tuková J, Clin Exp Rheumatol 2009; 27: 1047-1053

Υποδόρια και από του στόματος ΜΤΧ: σύγκριση στην κλινική αποτελεσματικότητα και ασφάλεια

Κλινική αποτελεσματικότητα της υποδόριας vs. της per os χορήγησης της MTX

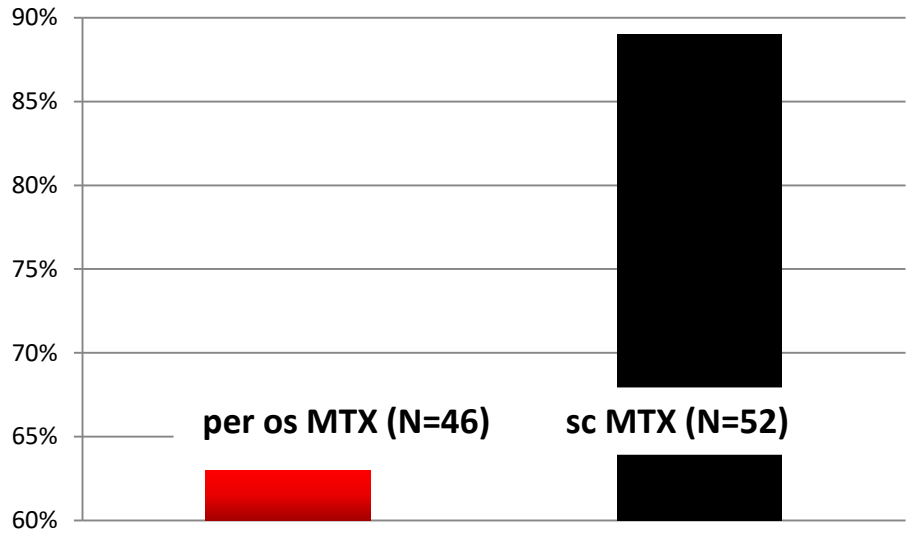
- Τυχαιοποιημένη διπλή τυφλή μελέτη
- 375 ασθενείς με ρευματοειδή αρθρίτιδα (DAS28 ≥4) τυχαιοποιήθηκαν είτε σε υποδόρια, είτε σε per os χορήγηση της ίδιας δόσης MTX

ACR20 (% ασθενών)



P<0.05 (24 εβδομάδες θεραπείας)

ACR20 (% ασθενών*)

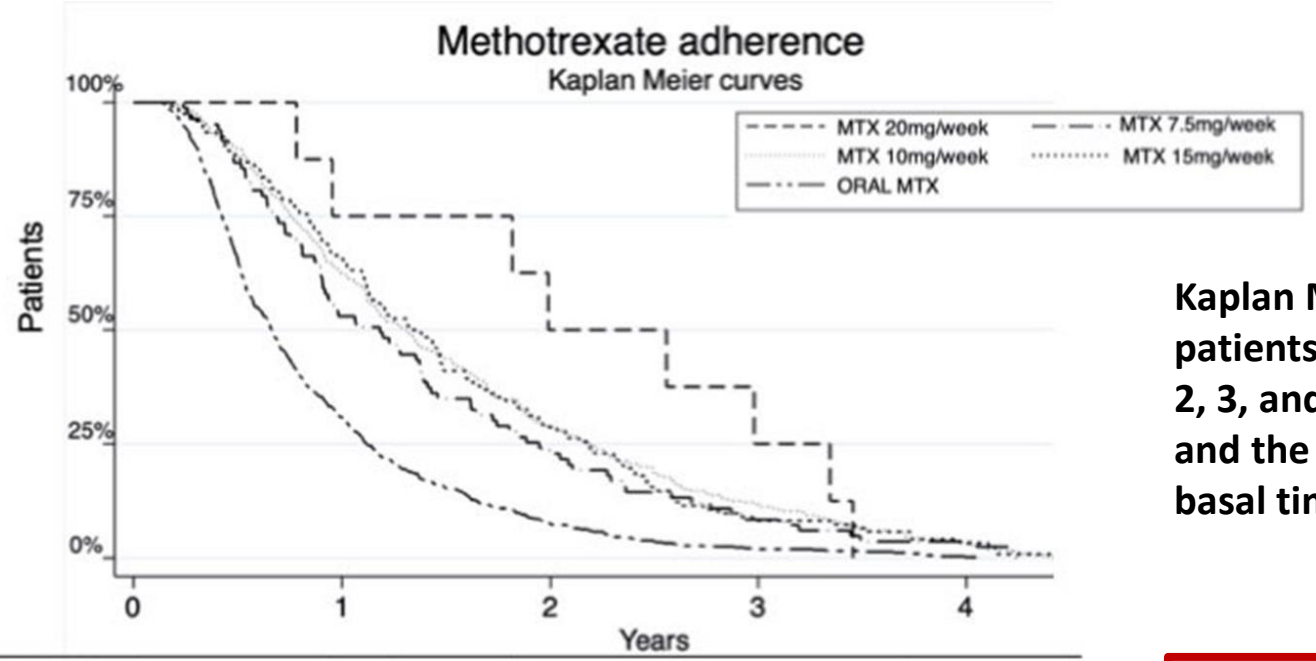


P<0.05 (24 εβδομάδες θεραπείας)

* Ασθενείς με διάρκεια νόσου > 1 έτος

Braun et al. *Arthritis Rheum* 2008;58:73-81

Non-adherence and discontinuation rate for oral and parenteral methotrexate: A retrospective-cohort study in 8,952 patients with psoriatic arthritis



Patients in MTX therapy, n (%)	Basal	1 year	2 years	4 years
Oral MTX	1,211 (100%)	363 (30%)	47 (3.9%)	8 (0.7%)
MTX 7.5mg/week	273 (100%)	184 (68%)	24 (8.8%)	8 (2.9%)
MTX 10mg/week	1,032 (100%)	753 (73%)	113 (10.9%)	31 (3.0%)
MTX 15mg/week	407 (100%)	289 (71%)	42 (10.3%)	11 (2.7%)
MTX 20mg/week	26 (100%)	20 (75%)	4 (15.4%)	0 (0%)

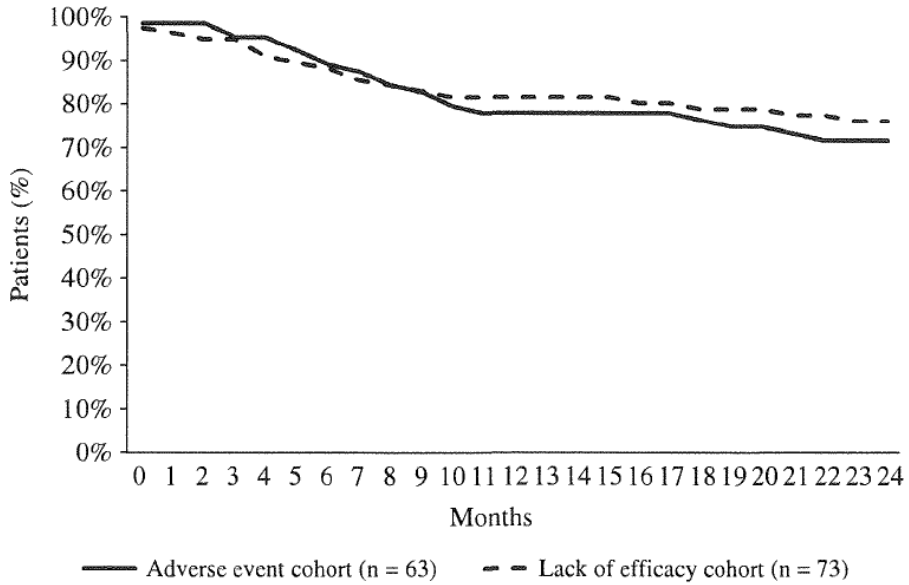
Kaplan Meier curves showing the proportion (%) of patients still taking MTX at different dosages after 1, 2, 3, and, 4 years. In the associated table the numbers and the percentages of the patients still taking MTX at basal time, after 1, 2, and, 4 years are reported.

Conclusion: **Oral MTX formulation is associated with a 2-fold risk of non-adherence compared to MTX parenteral route in PsA.**

Generali E, J Transl Autoimmun. 2021 Aug 16;4:100113

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

- Αναδρομική μελέτη όλων των ασθενών με ΡΑ στους οποίους είχε χορηγηθεί SC MTX σε συνέχεια της oral MTX στα Πανεπιστημιακά νοσοκομεία Norfolk και Norwich
- 196 άλλαξαν από oral σε SC MTX λόγω ανεπαρκούς δράσης (50.5%), ανεπιθύμητες ενέργειες (43.9%), ή άλλες αιτίες (5.6%). Πολύ υψηλός βαθμός παραμονής στην αγωγή διαπιστώθηκε με 83.0% των ασθενών σε SC MTX σε 1 έτος, 75.2% στα 2 έτη, και 47.0% στα 5 έτη.
- Μετά την αλλαγή σε SC MTX, < 10% των ασθενών έλαβαν βιολογική θεραπεία λόγω ανεπαρκούς απάντησης



Continuation rates for lack of efficacy and adverse event cohorts after initiation of SC MTX

Scott DGI, et al, Scand J Rheumatol 2014;43:470-476

Clin Rheumatol (2013) 32:1605–1612
DOI 10.1007/s10067-013-2318-z

ORIGINAL ARTICLE

Cost-minimisation analysis of subcutaneous methotrexate versus biologic therapy for the treatment of patients with rheumatoid arthritis who have had an insufficient response or intolerance to oral methotrexate

Ray Fitzpatrick · David GI Scott · Ian Keary

Η καθολική χρήση της SC MTX σε συνέχεια της αποτυχίας της MTX από του στόματος έχει την δυνατότητα να εξοικονομήσει £7,197 ανά ασθενή για το πρώτο έτος της θεραπείας

Fitzpatrick R, Clin Rheumatol. 2013;32:1605-12

RESEARCH ARTICLE

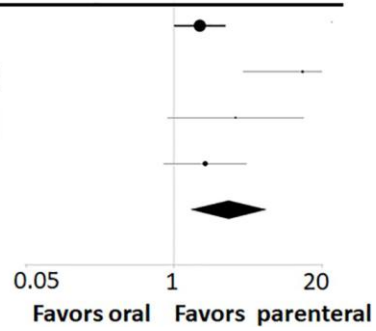
Comparison of oral versus parenteral methotrexate in the treatment of rheumatoid arthritis: A meta-analysis

Andreea M. Bujor[1]*, Sahar Janjua[1¤], Michael P. LaValley[2], Josefina Duran[3], Jürgen Braun[4], David T. Felson[1]

1 Department of Medicine, Boston University School of Medicine, Boston, Massachusetts, United States of America, 2 School of Public Health, Boston University, Boston, Massachusetts, United States of America, 3 Department of Clinical Immunology and Rheumatology, Pontificia Universidad Católica de Chile, Satinago, Chile, 4 Institut für angewandte Statistik Dr. Jörg Schnitker GmbH, Bielefeld, Germany

Μετα-ανάλυση: Σύγκριση από του στόματος έναντι παρεντερικής MTX στη PA

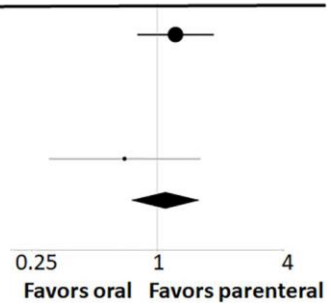
Study	Oral		Parenteral			Odds ratio, 95% CI
	Patients with ACR20	Total patients	Patients with ACR20	Total patients	Weight	
Braun (2008)	143	187	159	188	56%	1.69 [1.00, 2.84]
Ahmed (2010)	4	44	23	40	12%	13.53 [4.06, 45.10]
Islam (2013)	37	46	43	46	9%	3.49 [0.88, 13.84]
Dhaon (2016)	21	45	28	45	23%	1.88 [0.81, 4.36]
Total	205	322	250	319	100%	3.02 [1.41, 6.46]



Summary OR for achieving ACR20 using parenteral vs. oral MTX

The summary OR for achieving ACR20 using parenteral vs. oral MTX was 3.02 (95% CI 1.41, 6.46), with no significant difference in the risk for all adverse events

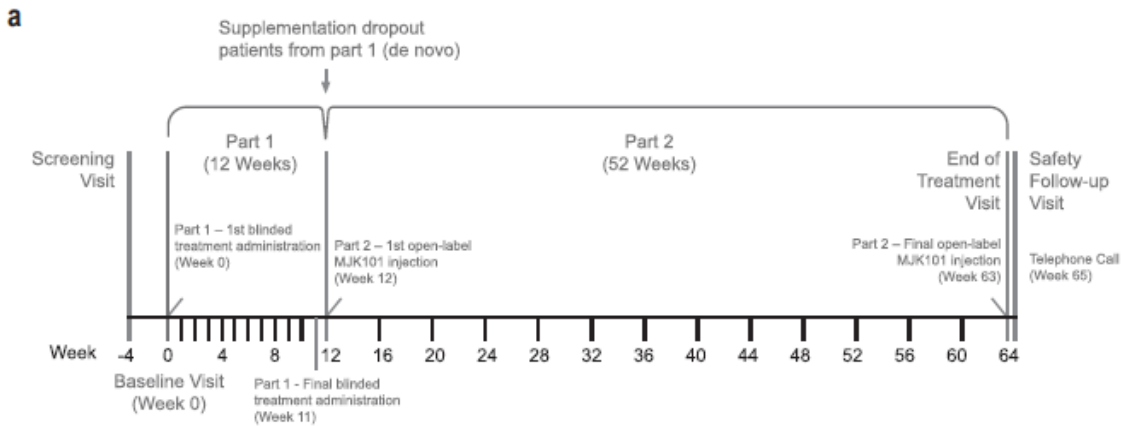
Study	Oral		Parenteral		Weight	Odds ratio, 95% CI
	Patients with any AEs	Total patients	Patients with any AEs	Total patients		
Braun (2008)	116	188	128	193	80%	1.22 [0.80, 1.86]
Ahmed (2010)						
Islam (2013)						
Dhaon (2016)	22	45	18	45	20%	0.70 [0.30, 1.61]
Total	138	233	146	238	100%	1.09 [0.75, 1.59]



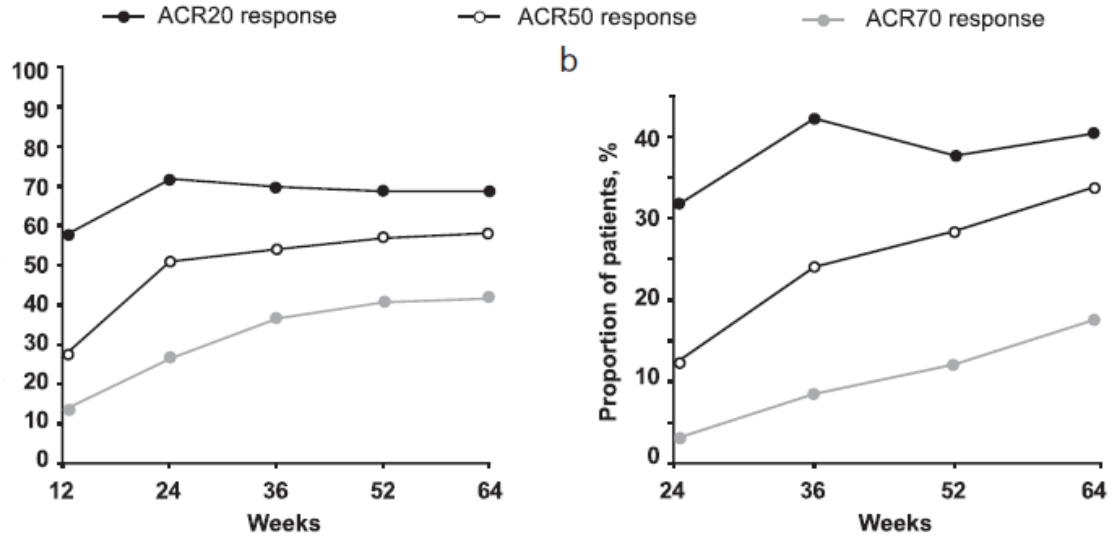
Summary OR for adverse effects data (any AE)

Bujor AM, PLoS ONE 2019: 14(9): e0221823

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



MTX-naïve patients were randomized in a 1:1 ratio to receive a 12-week administration of either 7.5 mg MTX subcutaneously (MJK101, a prefilled syringe for subcutaneous injection) or 8 mg MTX orally in Part 1 of the trial. The primary end point was a 20% improvement in the American College of Rheumatology criteria (ACR20) at Week 12. In the second part, all enrolled patients received MJK101 weekly for 52 weeks with doses starting from 7.5 to 15 mg with 2.5 mg increments with the option of self-administration of MJK101



ACR20, ACR50, and ACR70 responders (proportion of FAS) at Weeks 12, 24, 36, and 64, treated with MJK101. (a) ACR20, ACR50, and ACR70 for the total rollover patients (N = 98) compared to the baseline of Part 1 (prior to the start of treatment at Week 0). (b) ACR20, ACR50, and ACR70 for all patients enrolled in Part 2 (rollover and de novo patients directly included in Part 2, N = 109) compared to the baseline of Part 2 (Week 12).

Tanaka Y, Modern Rheumatology, 33, 2023, 680–689

Rheumatology, 2025, **00**, 1–8
https://doi.org/10.1093/rheumatology/keaf054
Advance access publication 7 February 2025
Original Article

British Society for Rheumatology RHEUMATOLOGY OXFORD

Clinical science

Comparison of the efficacy and safety of methotrexate injection and methotrexate tablets in active RA

ACR20, ACR50 and ACR70 response rates at week 4, 8 and 12. ACR20/50/70 represent achievements of a response according to the American College of Rheumatology criteria for 20%/50%/70% improvements. The response of ACR70 in OR MTX group is 0. W: week

The safety profile of SC MTX is similar to that of OR MTX in general, and the incidence, occurrences and preferred term types of drug-related TEAE of gastrointestinal system disorders were lower.

Qiao L, Rheumatology (Oxford). 2025 Feb 7:keaf054

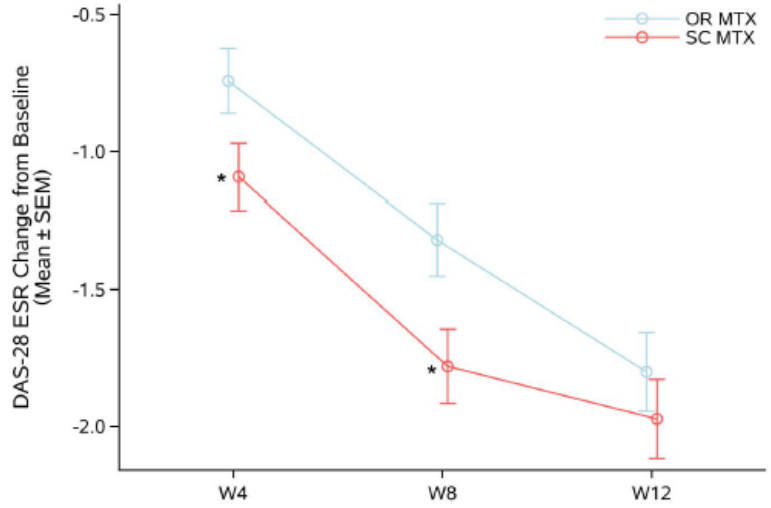


Figure 2. Changes in DAS28-ESR scores from baseline to week 4, 8 and 12 between the two groups. Changes in DAS28-ESR scores from baseline to week 4 and 8 between the two groups are statistically significant. W: week. *, $P < 0.05$

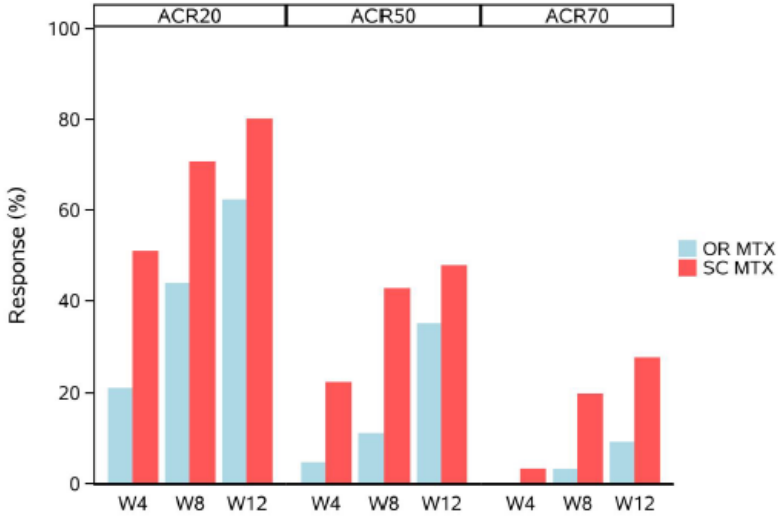


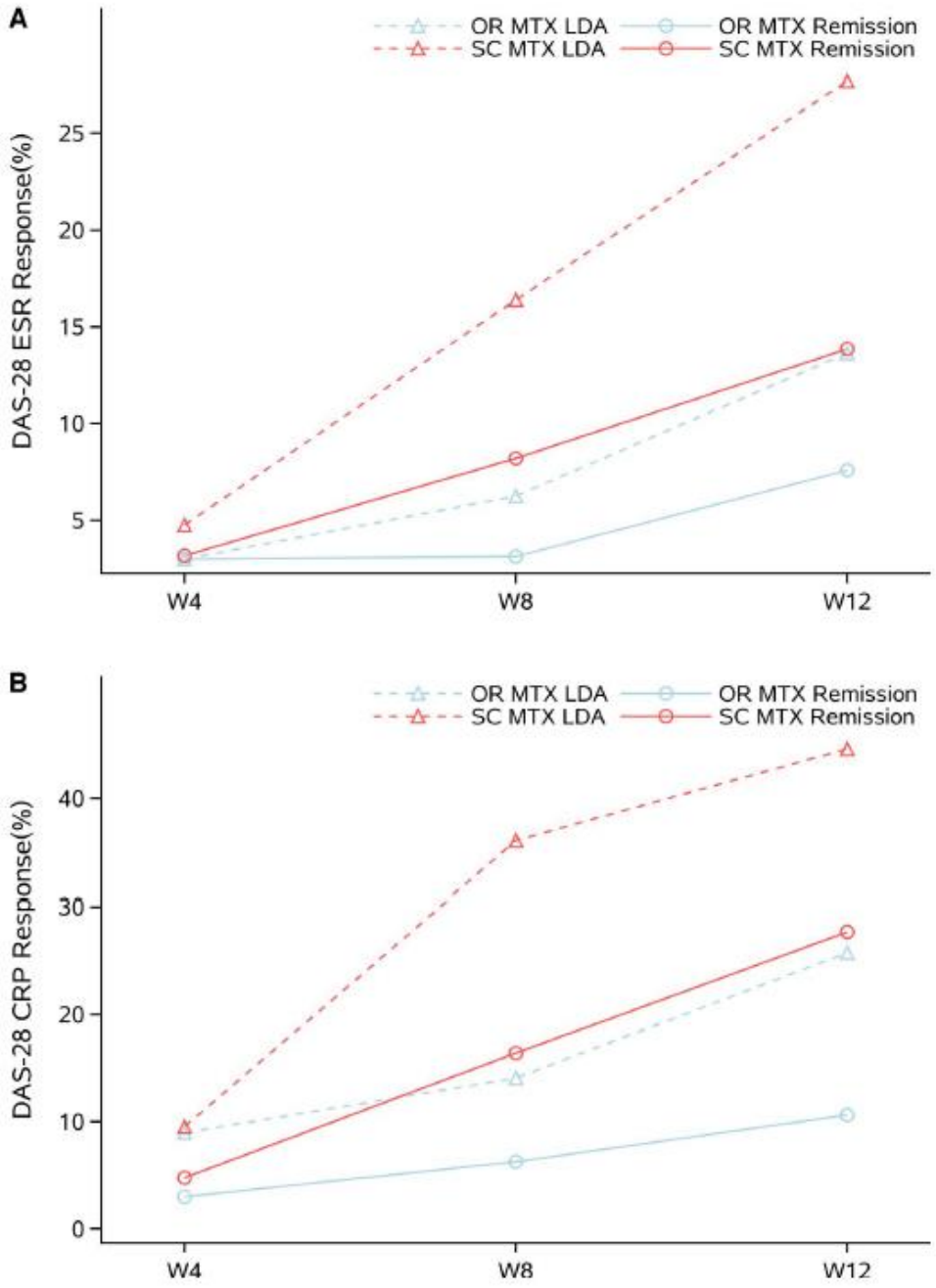
Figure 3. ACR20, ACR50 and ACR70 response rates at week 4, 8 and 12. ACR20/50/70 represent achievements of a response according to the American College of Rheumatology criteria for 20%/50%/70% improvements. The response of ACR70 in OR MTX group is 0. W: week

Rheumatology, 2025, **00**, 1–8
https://doi.org/10.1093/rheumatology/keaf054
Advance access publication 7 February 2025
Original Article

British Society for Rheumatology RHEUMATOLOGY OXFORD

Clinical science

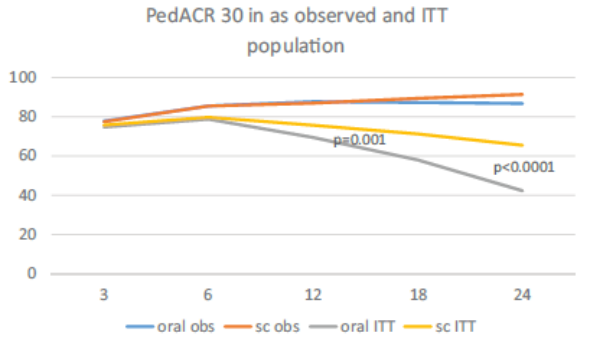
Comparison of the efficacy and safety of methotrexate injection and methotrexate tablets in active RA

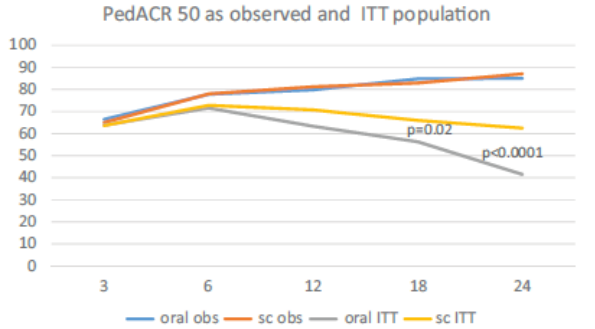


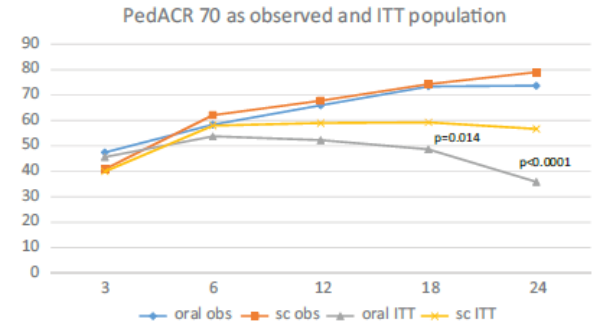
The proportion of patients who achieved LDA and disease remission at week 4, 8 and 12 evaluated by the DAS28-ESR and DAS28-CRP. (A) DAS28-ESR response represented the patients who achieved LDA and disease remission measured by CRP. (B) DAS28-CRP response represented the patients who achieved LDA and disease remission measured by ESR. The proportion of patients reaching a DAS28-ESR/CRP score of ≤3.2 was classified as low disease activity (LDA), whereas that with scores of ≤2.6 was classified as disease remission

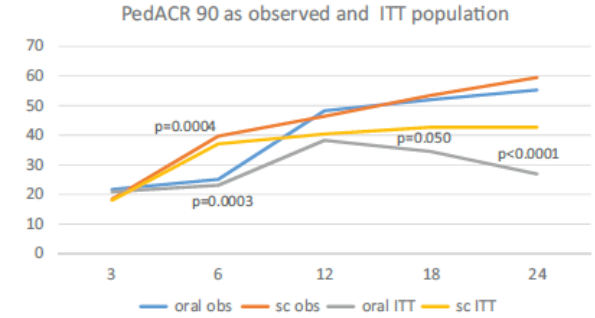
Qiao L, Rheumatology (Oxford). 2025 Feb 7:keaf054

Oral or Parenteral Methotrexate for the Treatment of Polyarticular Juvenile Idiopathic Arthritis

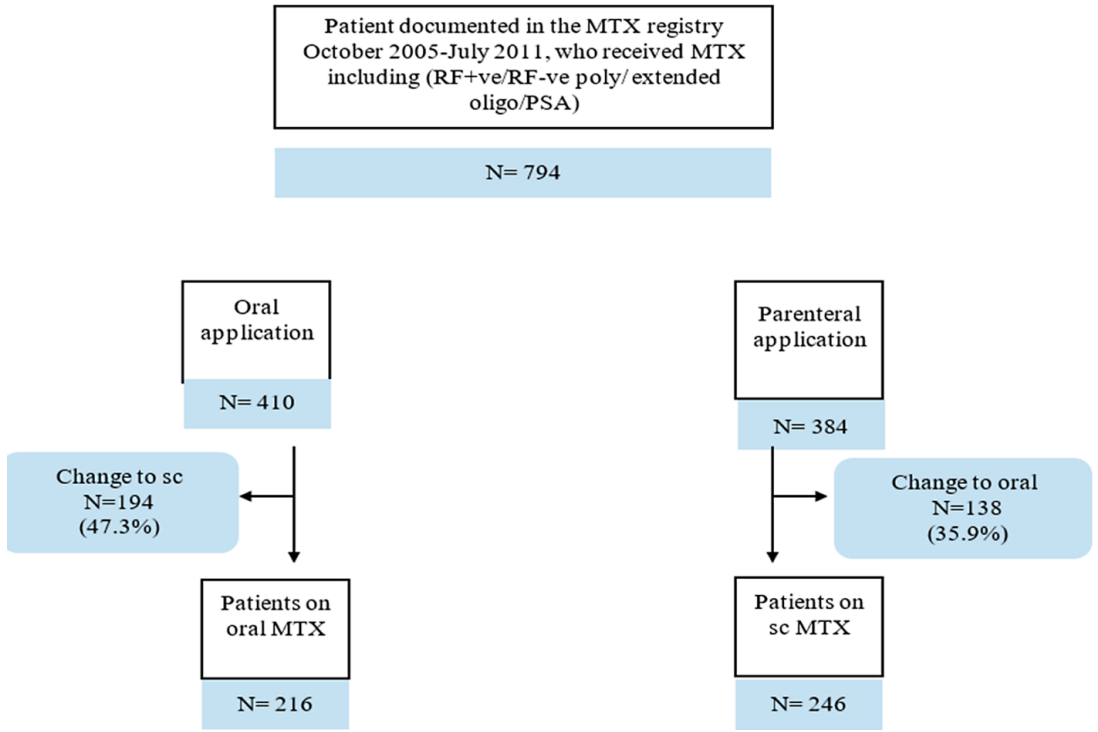




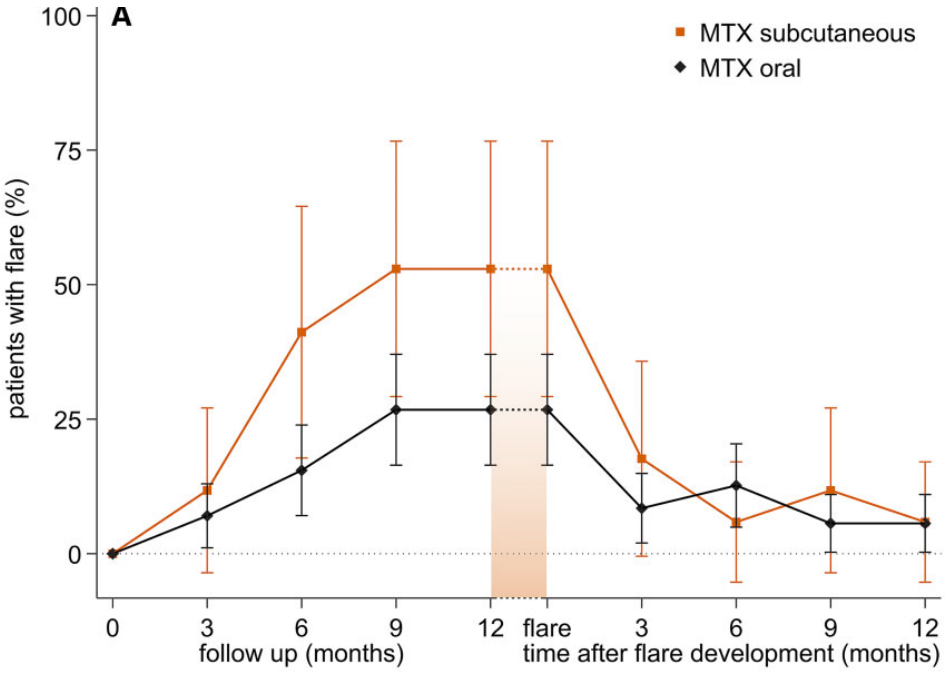


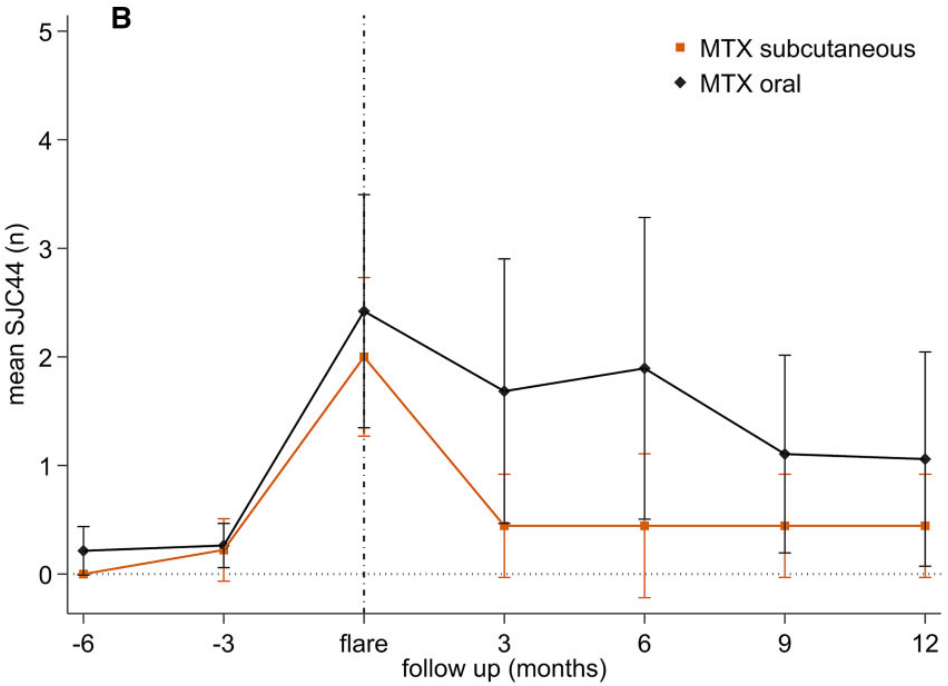


PedACR 39/50/70/ped90 response rates among oral and s.c. MTX cohorts in the as-observed and intention to treat population. At month 24 of treatment, the response rate was higher in the s.c. cohort in the intention to treat population (*P* < .0001, HR = 2.6 [1.8-3.7]) for PedACR 30; *P* < .0001, HR = 2.4 [1.65-3.34]) for PedACR 50; *P* < .0001, HR = 2.3 [1.64-3.32] for PedACR 70; *P* < .0001, HR = 2.02 [1.4-2.3] for PedACR 90)



Bakry R, *Eur J Rheumatol.* 2022;9(4):197-205





Tapering subcutaneous methotrexate causes more disease flares compared with tapering oral administration in established rheumatoid arthritis patients

(A) The first part on the x-axis illustrates the cumulative percentage of patients who develop a disease flare during follow-up. The second part illustrates the cumulative percentage of patients who still have active disease (DAS >2.4 and SJC44 >1) from the point of flare development and after restarting the last effective treatment. (B) Mean SJC44 before, during and after development of a disease flare.

Agnes E.M. Looijen, Rheumatology 2022;61:e216–e218

MEDITERRANEAN JOURNAL OF RHEUMATOLOGY | 35 1 2024

ORIGINAL PAPER

Should All Patients Trial Subcutaneous Methotrexate Prior to Commencing Biologic Therapy? A Real World Study

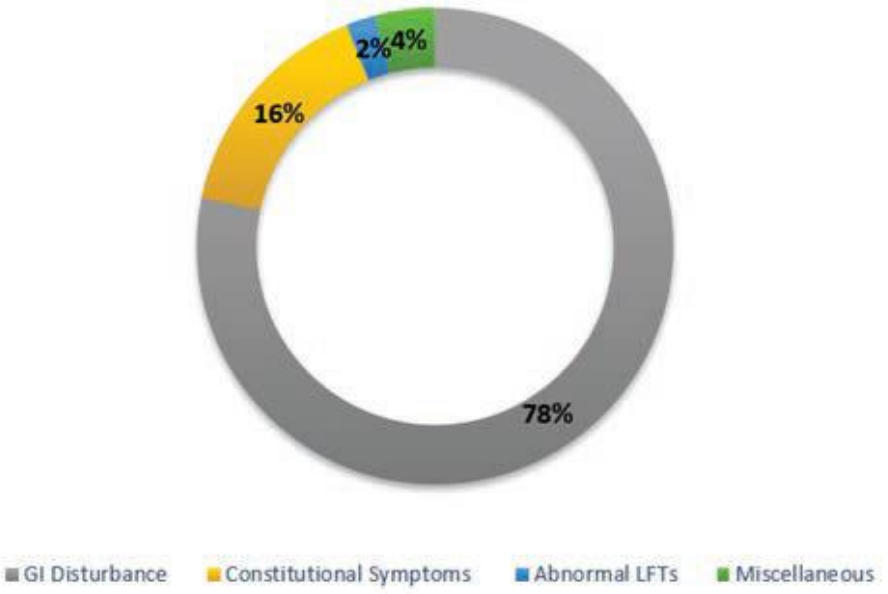
Anem Mirza, Muhammad K. Nisar

Department of Rheumatology, Luton & Dunstable University Hospital NHSFT, Luton, United Kingdom

A retrospective survey of patients prescribed SC MTX in a university teaching hospital identified 352 patients. 298 switched from oral to SC MTX- 164 stopped oral MTX due to side effects, 134 stopped due to inefficacy, and 54 started SC MTX as first line therapy. 103 patients progressed to biologic therapy.

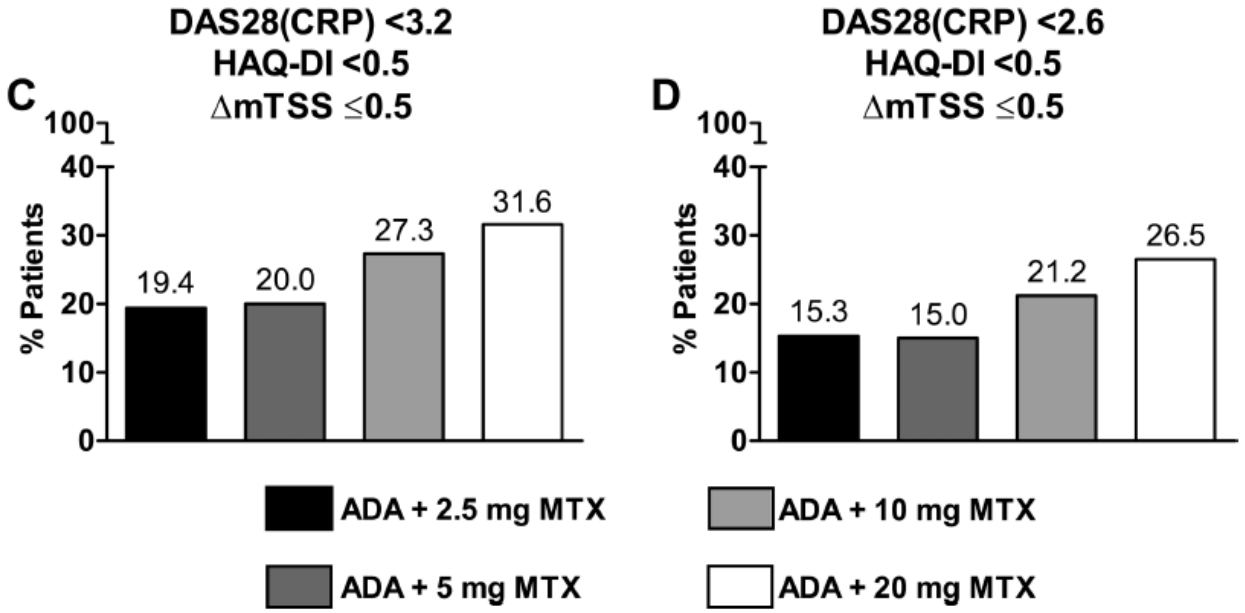
Rheumatoid arthritis (RA): DAS-28 improved from a mean of 4.06 (0.63-8.06) to 2.83 (0.14-7.32) following the switch (p<0.0001). Psoriatic arthritis (PsA): total joint count improved from a mean of 7 (0-42) to 2 (0-25) (p<0.0001). Swollen joint count improved from a mean of 2 (0-26) to 1 (0-6) (p=0.09). Discussion: SC MTX is an effective solution for RA and PsA, irrespective of whether oral MTX is inefficacious or intolerable. Where oral MTX was ineffective, a switch to SC achieved low disease activity despite multi-morbidity, long disease course and protracted oral MTX exposure. This intervention prevented over two-thirds of patients requiring biologics. SC MTX is a durable strategy with excellent disease outcomes and substantial economic benefits.

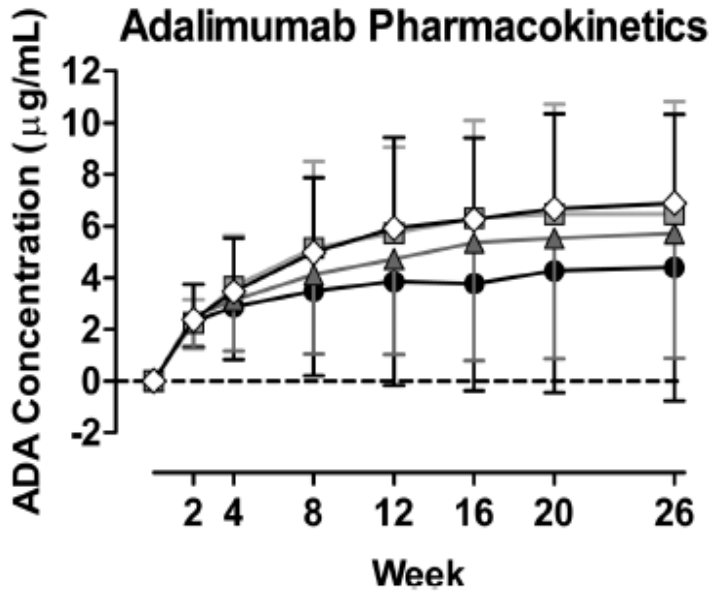
Adverse effects experienced by patients on oral MTX



Mediterr J Rheumatol 2024;35(1):115-22

Efficacy and safety of ascending methotrexate dose in combination with adalimumab: the randomised CONCERTO trial





- RCT με MTX-naïve ασθενείς με αρχική ταυτόχρονη χορήγηση Adalimumab 40mg/2w
- 4 ομάδες των 100 ασθενών περίπου με 5, 7.5, 10 και 20mg MTX per os
- Δεν διαπιστώθηκε σημαντική διαφορά μεταξύ των ομάδων 10 και 20mg MTX

Burmester G-R, et al. Ann Rheum Dis 2015;74:1037-44

The issue of bioavailability of oral low dose methotrexate: should we choose only 10 mg of MTX a week in conjunction with anti-TNF therapy?

- Οι ασθενείς ήταν MTX-naive και έλαβαν ταυτόχρονα Adalimumab και MTX σε αντίθεση με την κλινική πράξη
- Η MTX δόθηκε per os σε μία δόση, γεγονός που μειώνει σαφώς την απορρόφηση των 20mg
- Η βιοδιαθεσιμότητα λόγω διαφοράς στην απορρόφηση της MTX από του στόματος ποικίλει από 30% έως 90% της χορηγηθείσας δόσης
- Έχει αποδειχθεί ότι ήδη στα 15mg per os εβδομαδιαία δόση η απορρόφηση μειώνεται κατά 30%, με σύσταση 2 δόσεων και μεσοδιάστημα >12h
- Για πραγματική αξιολόγηση μεγαλύτερων δόσεων MTX ο συγγραφέας προτείνει υποδόρια χορήγηση ≥15mg, ώστε να μπορεί να συγκριθεί με τα 10mg από του στόματος

Zeidler H. Ann Rheum Dis 2014;73:e50

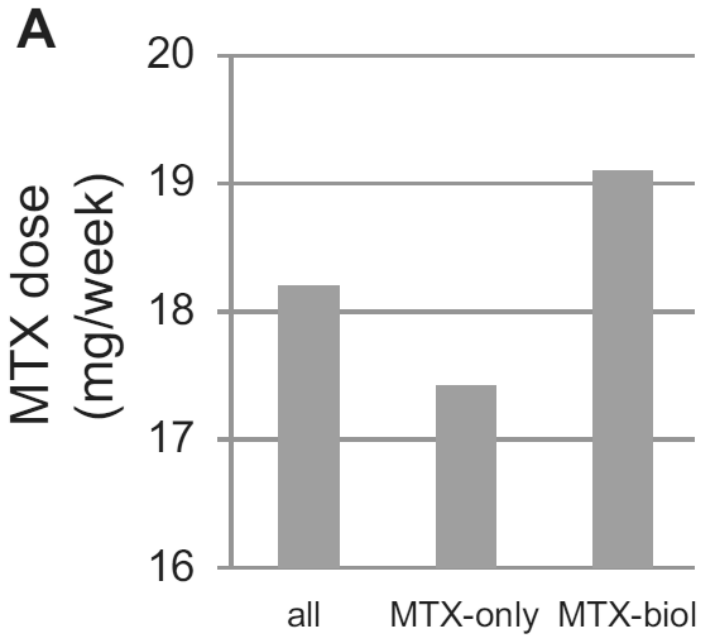
Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

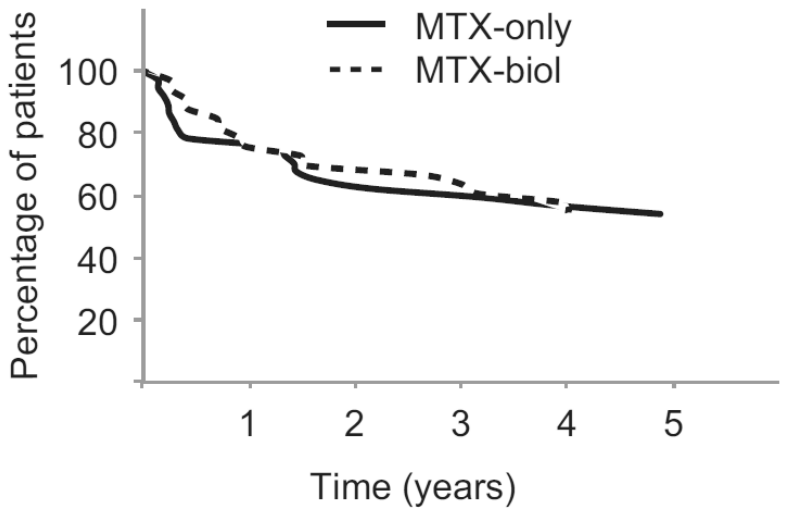
journal homepage: www.elsevier.com/locate/semarthrit

Effectiveness, tolerability, and safety of subcutaneous methotrexate in early rheumatoid arthritis: A retrospective analysis of real-world data from the St. Gallen cohort

Δόσεις υποδόριας MTX



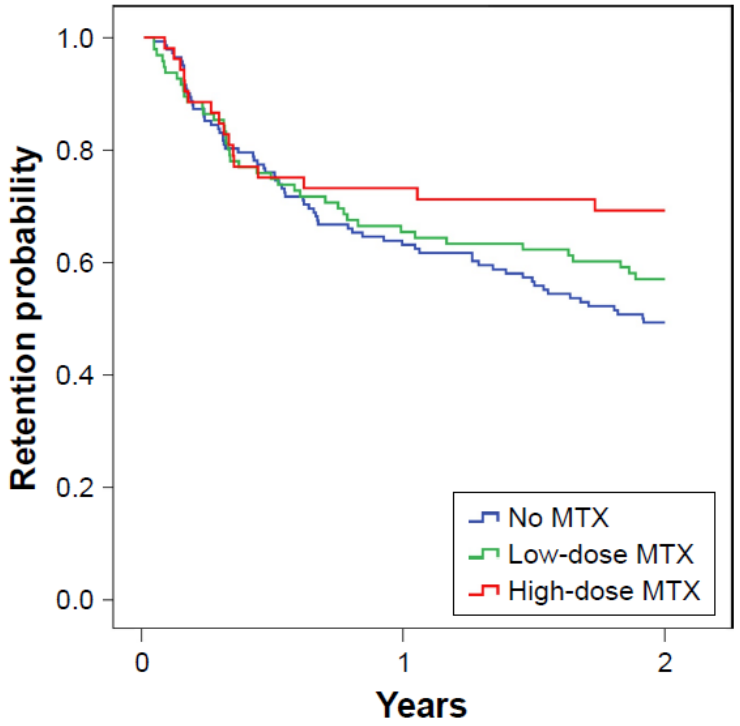
Συχνότητα διακοπής



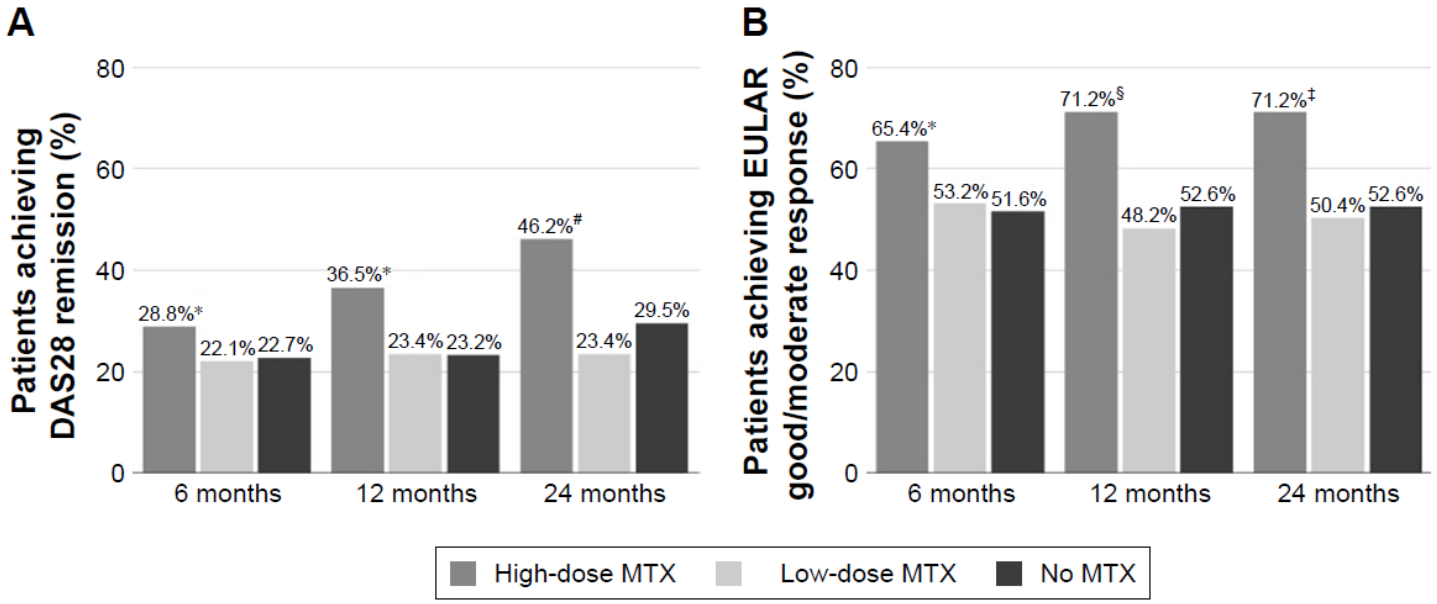
R.B. Müller et al, Semin Arthritis Rheum 2015;45:28-34

The role of concomitant methotrexate dosage and maintenance over time in the therapy of rheumatoid arthritis patients treated with adalimumab or etanercept: retrospective analysis of a local registry

Δόση MTX στο συνδυασμό με αντι-TNF αγωγή και μακροχρόνια έκβαση



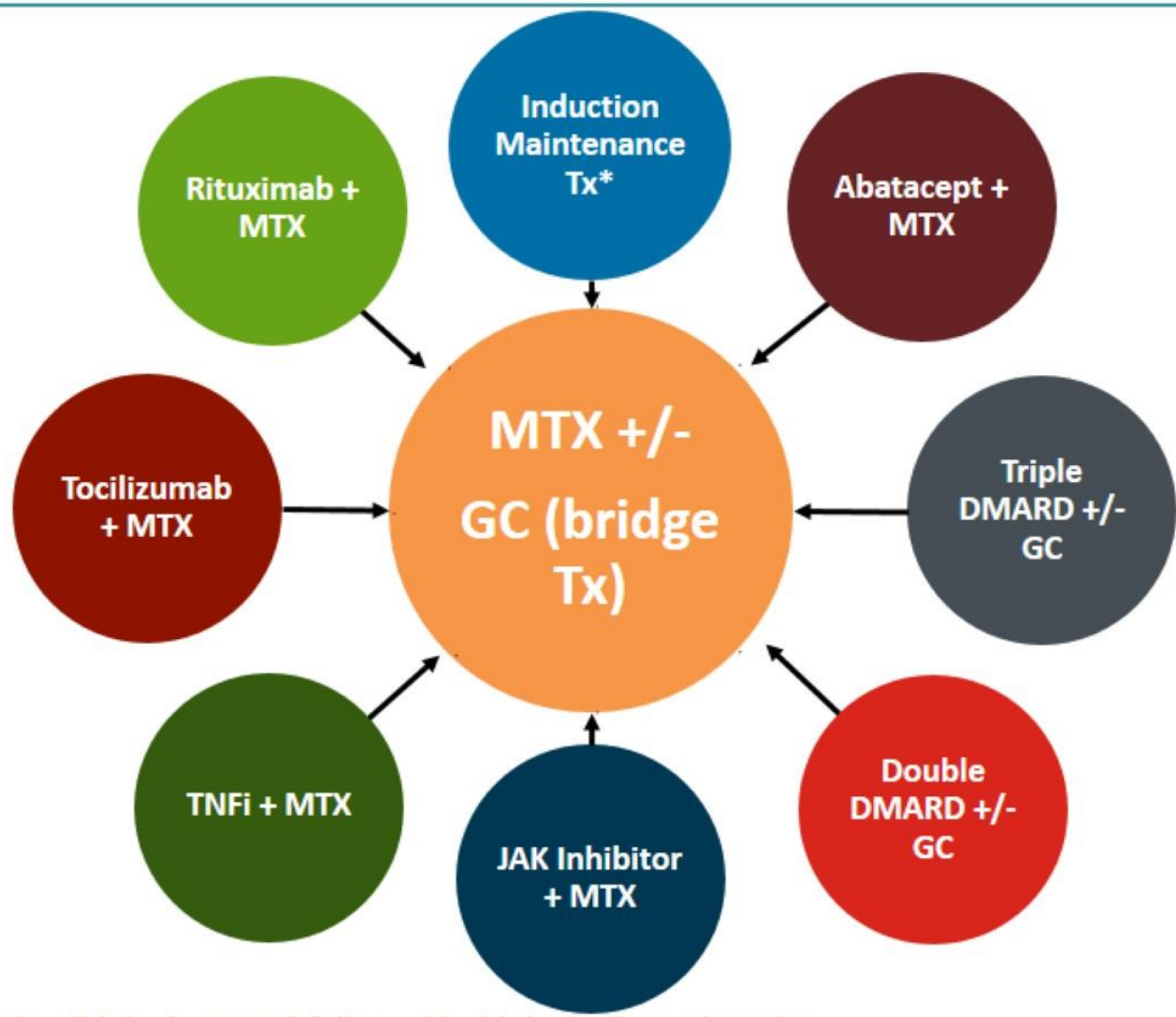
Two-year drug survival of TNFi treatment according to maintenance of baseline concomitant MTX regimen



The impact of maintenance of baseline concomitant MTX regimen on (A) DAS 28 remission and (B) European League Against Rheumatism good/moderate clinical response

Favalli EG, Drug Des Devel Ther. 2018;12:1421-1429

Different RA Combination Treatments Centered on MTX



*Initial combination (biologic + MTX) followed by biologic discontinuation

Graudal N, et al. *PLoS One*. 2014;9:e106408.

RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Methotrexate effect on immunogenicity and long-term maintenance of adalimumab in axial spondyloarthritis: a multicentric randomised trial

MTX και ανοσογονικότητα βιολογικών παραγόντων

Table 1 Baseline characteristics of the 107 patients with axial spondyloarthritis who received adalimumab with or without MTX (n=107)

	MTX+ (n=52)	MTX– (n=55)	P value
Sex, male	22 (42)	28 (51)	0.48
HLA B27-positive	30 (58)	33 (60)	0.78
Age (years)	43(18-71)	41(18-65)	0.61
BMI (kg/m^2)	25(18-35)	27(17-40)	0.24
Disease duration (years)	3 (0–34)	2 (0–41)	0.93
Previous TNF inhibitor	12 (23)	8 (15)	0.38
ASDAS	3.0 (1.0–5.4)	3.2 (1.5–5.0)	0.70
CRP level (mg/L)	2.5 (0–65)	4 (0–57)	0.50

- **107 ασθενείς με αξονική σπονδυλαρθροπάθεια**
- **Τυχαιοποίηση 1:1**
- **2 εβδ πριν το adalimumab και μετά ανά εβδ, MTX 10 mg υποδορίως (MTX+) ή όχι (MTX–)**

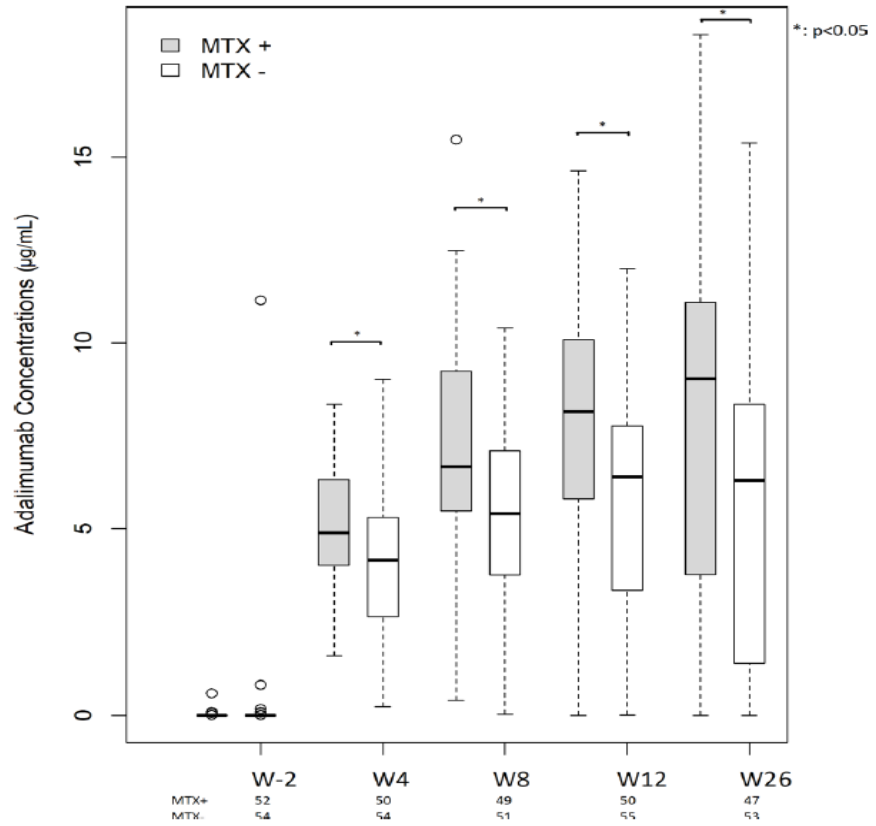
Ducourau E, *RMD Open* 2020;6:e001047

RMD Open
Rheumatic & Musculoskeletal Diseases

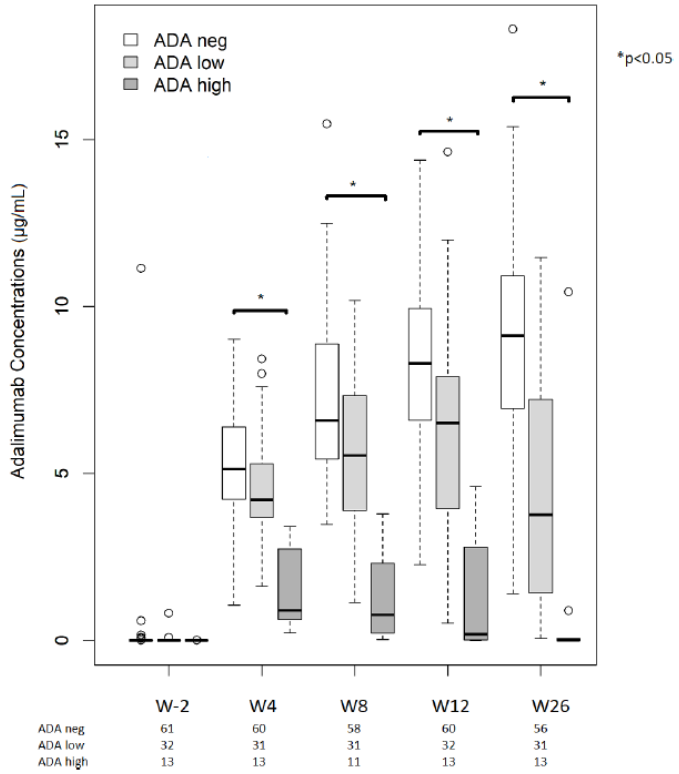
ORIGINAL RESEARCH

Methotrexate effect on immunogenicity and long-term maintenance of adalimumab in axial spondyloarthritis: a multicentric randomised trial

MTX και ανοσογονικότητα βιολογικών παραγόντων



Επίπεδα adalimumab σε σχέση με την λήψη ή μη, MTX



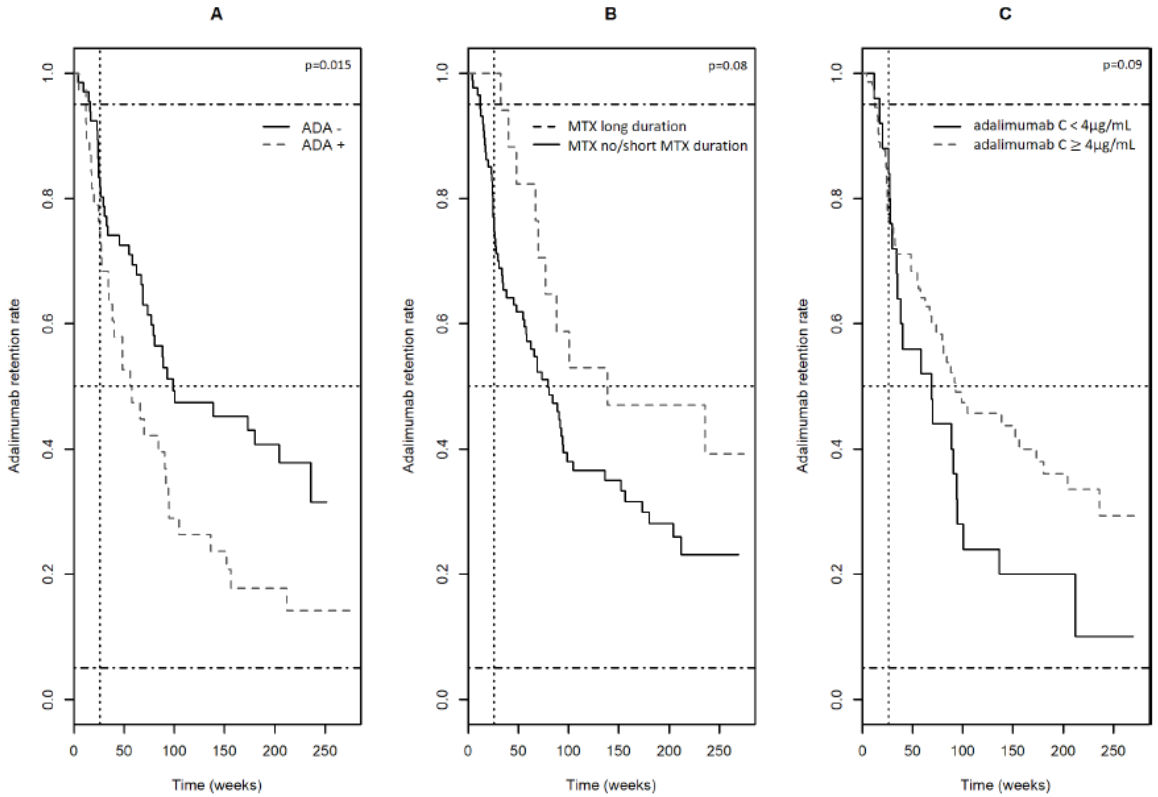
Επίπεδα adalimumab σε σχέση με τα επίπεδα αντισωμάτων έναντι του φαρμάκου και την λήψη ή μη, MTX

Ducourau E, *RMD Open* 2020;6:e001047

RMD Open
Rheumatic & Musculoskeletal Diseases
ORIGINAL RESEARCH

Methotrexate effect on immunogenicity and long-term maintenance of adalimumab in axial spondyloarthritis: a multicentric randomised trial

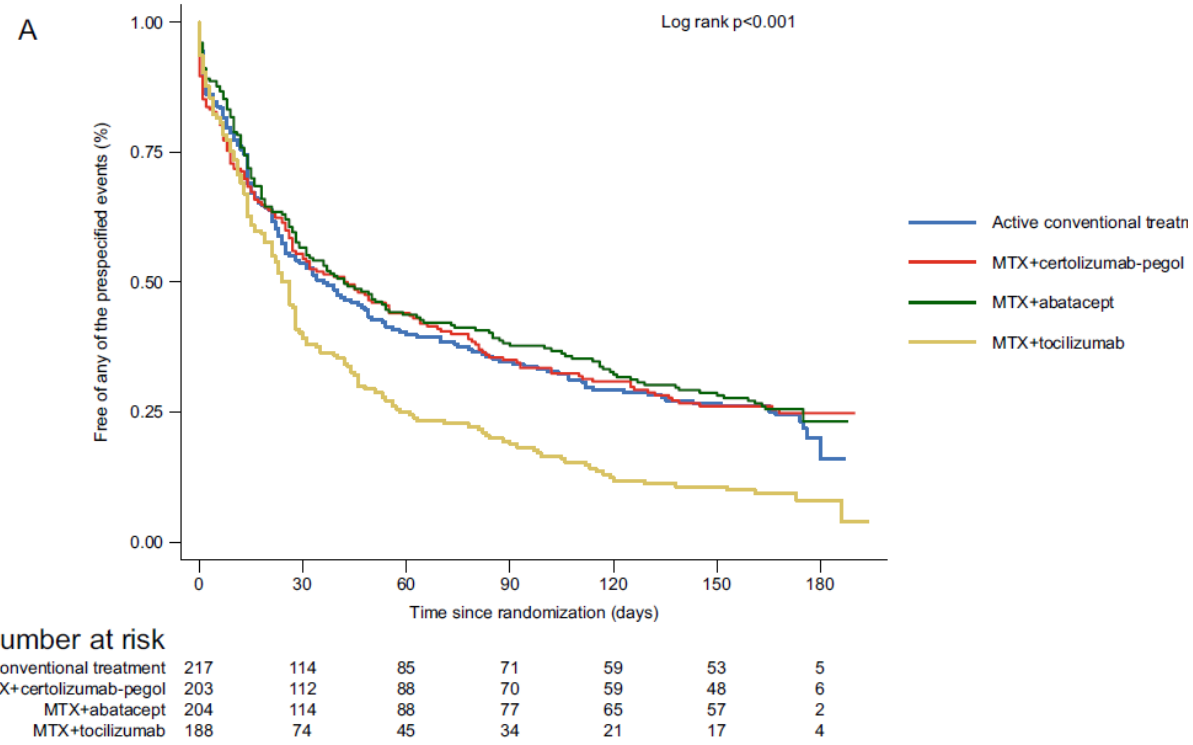
MTX, ανοσογονικότητα βιολογικών παραγόντων και μακροχρόνια παραμονή στη θεραπεία

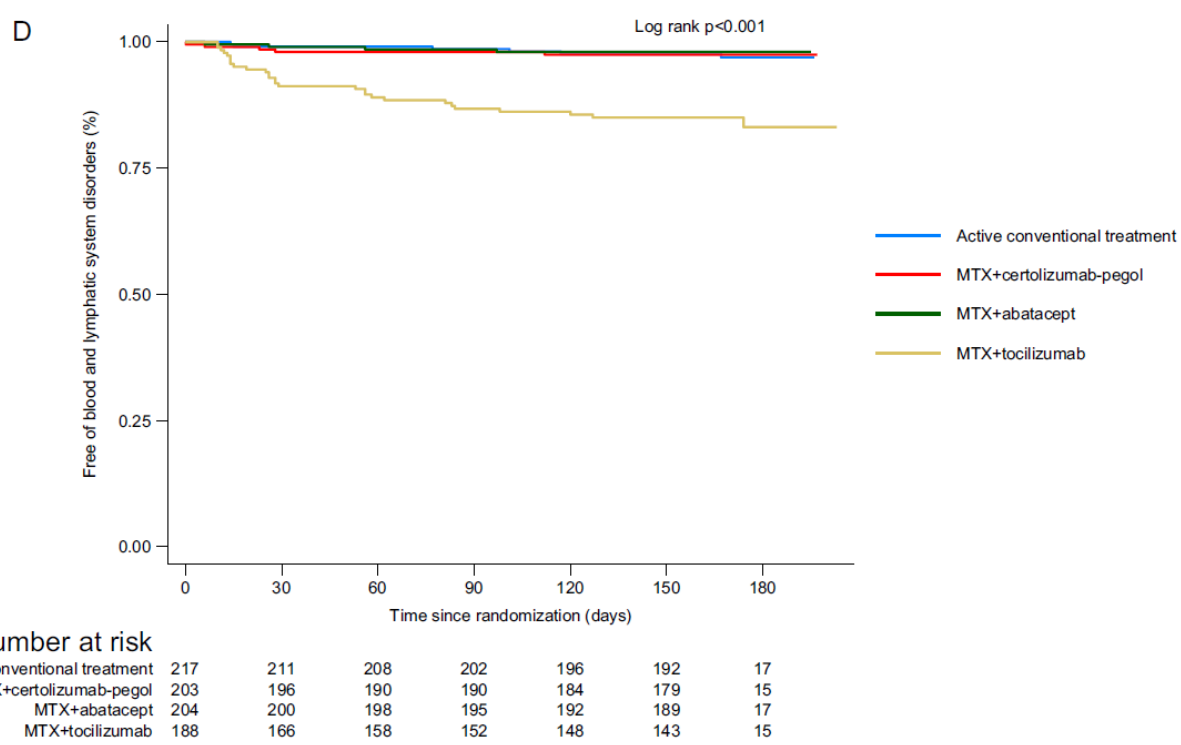


Adalimumab maintenance according to (A) anti-drug antibody (ADA)+ versus ADA− at week 26 (W26), (B) methotrexate (MTX) long duration, that is >W26, versus no MTX or MTX short duration, that is ≤W26 and (C) adalimumab concentrations<1st quartile at W8, that is <4 µg/mL, versus adalimumab concentration ≥1st quartile, that is ≥4 µg/mL

Ducourau E, *RMD Open* 2020;6:e001047

Methotrexate Safety and Efficacy in Combination Therapies in Patients With Early Rheumatoid Arthritis: A Post Hoc Analysis of a Randomized Controlled Trial





Adverse event of interest plot by Kaplan-Meier estimators for the time from randomization until 24 weeks visit (median day 168, interquartile range 167–174, target date by the NORD-STAR protocol day 168 ± 1 week) by treatment group. Data include the first event of a given type. Patients for whom no events were observed were censored at 24 weeks visit or at the time of withdrawal. MTX, methotrexate. (A) Free of any of the prespecified events. (D) Free of blood and lymphatic system disorders.

Lend K, Arthritis Rheumatol. 2024;76(3):363-376

Recommendation

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update

Οι 11 συστάσεις της EULAR στη PA

1.	Therapy with DMARDs should be started as soon as the diagnosis of RA is made.	1a	A
2.	Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient.	1a	A
3.	Monitoring should be frequent in active disease (every 1–3 months); if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted.	2b	B
4.	MTX should be part of the first treatment strategy.	1a	A
5.	In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy.	1a	A
6.	Short-term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered and discontinued as rapidly as clinically feasible.	1a	A
7.	If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors, other csDMARDs should be considered.	5	D
8.	If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, a bDMARD should be added; JAK-inhibitors may be considered, but pertinent risk factors* must be taken into account.	Efficacy: 1a; Safety: 1b	Efficacy: A; Safety: B
9.	bDMARDs and tsDMARDs* should be combined with a csDMARD; in patients who cannot use csDMARDs as comedication, IL-6 pathway inhibitors and tsDMARDs* may have some advantages compared with other bDMARDs.	Efficacy: 1a	Efficacy: A
10.	If a bDMARD or tsDMARD* has failed, treatment with another bDMARD or a tsDMARD*$^{+}$ should be considered; if one TNF or IL-6 receptor inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF-/ IL-6R-inhibitor^{++}.	Efficacy: 1a/$^{+}$5/$^{++}$3; safety: 1b	Efficacy: A/$^{+}$D; Safety: B; IL-6R-inhibition: C
11.	After glucocorticoids have been discontinued and a patient is in sustained remission, dose reduction of DMARDs (bDMARDs/tsDMARDs* and/or csDMARDs) may be considered.	1b	A

Smolen JS, Ann Rheum Dis 2023;82:3–18

Recommendation

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update

4. *Methotrexate (MTX) should be part of the first treatment strategy*

"MTX should be used in any case, unless not tolerated or contraindicated, such as in patients with significant renal impairment.

- The Task Force had also no route-of-administration preference, although costs have to be considered in line with overarching principle E.

- In the presence of sufficient folic acid supplementation, MTX can be rapidly escalated to about 25 mg once weekly (in line with a relative dose of 0.3 mg/kg body weight for a person of about 80 kg;"

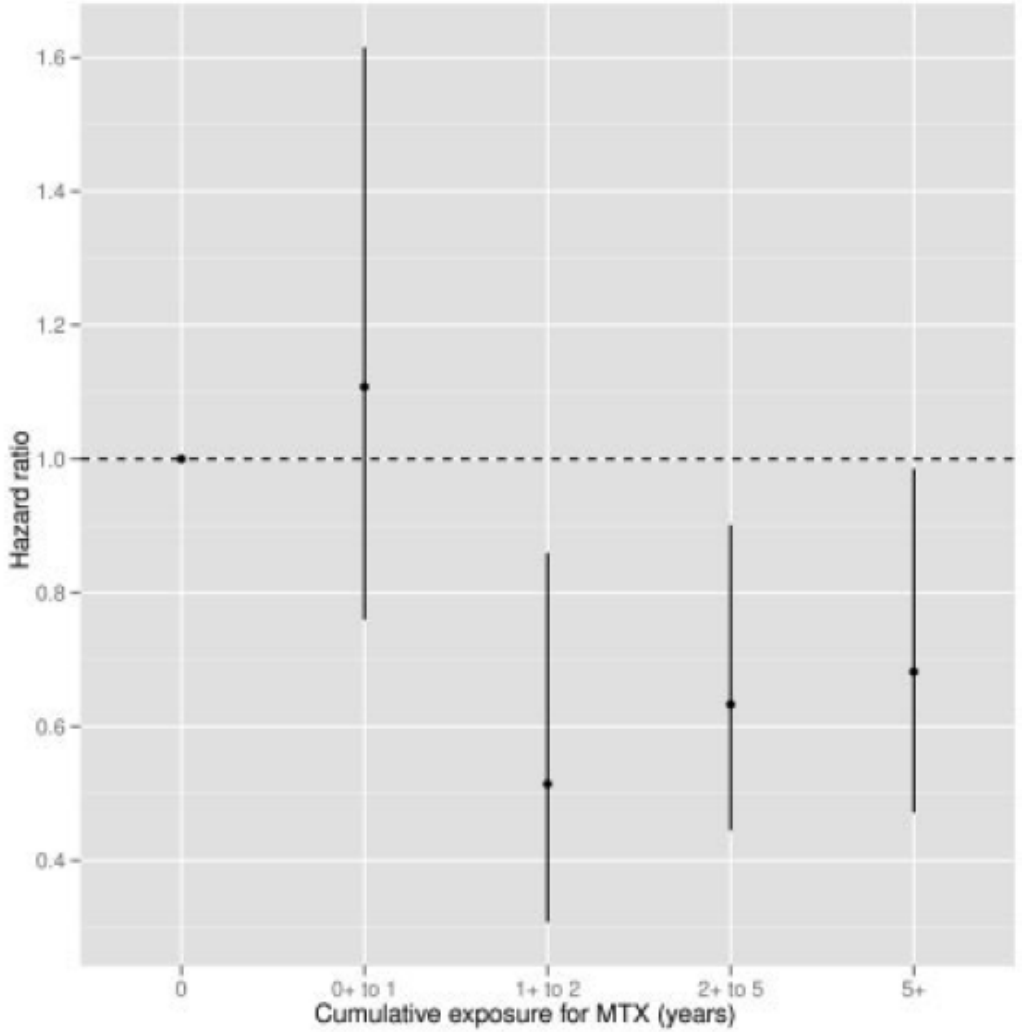
Smolen JS, Ann Rheum Dis 2023;82:3–18

MTX: Τι νεότερο στην ασφάλεια

MTX και επιβίωση στην PA

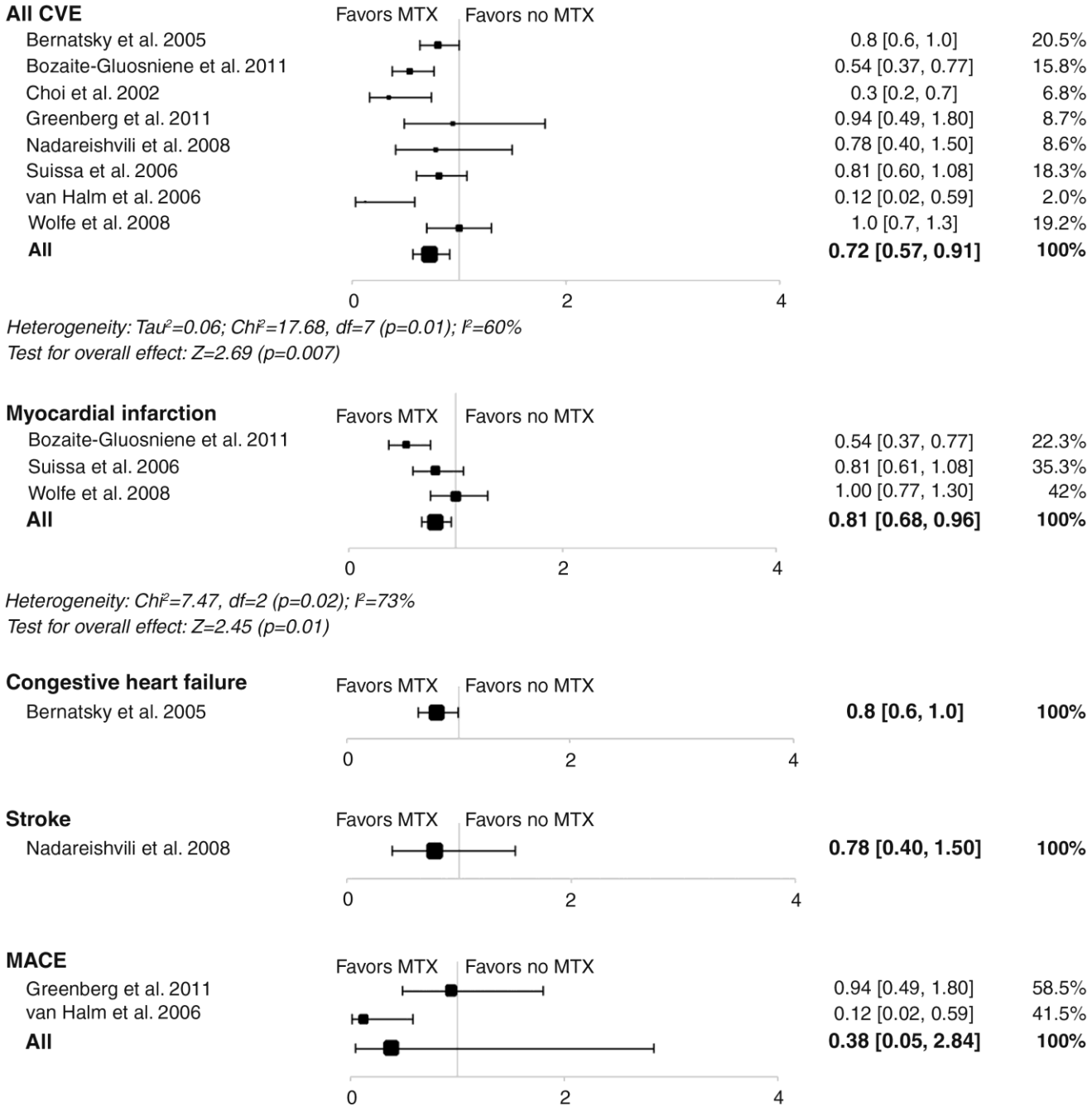
Propensity-Adjusted Association of Methotrexate With Overall Survival in Rheumatoid Arthritis

Mary Chester M. Wasko,[1] Abhijit Dasgupta,[2] Helen Hubert,[3] James F. Fries,[4] and Michael M. Ward[2]



- 5626 ασθενείς με PA παρακολούθηση για 25 έτη, 666 θάνατοι στο διάστημα αυτό
- Η χρήση της MTX για διάστημα μεγαλύτερο του έτους διαπιστώθηκε ότι συνδυάζεται με μείωση της θνητότητας κατά 70%

Wasko MC, Arthritis Rheum. 2013;65:334-42



MTX και καρδιακά συμβάματα σε ΡΑ, ΨΑ και ψωρίαση

CVE= cardiovascular event
MACE= major adverse cardiac event

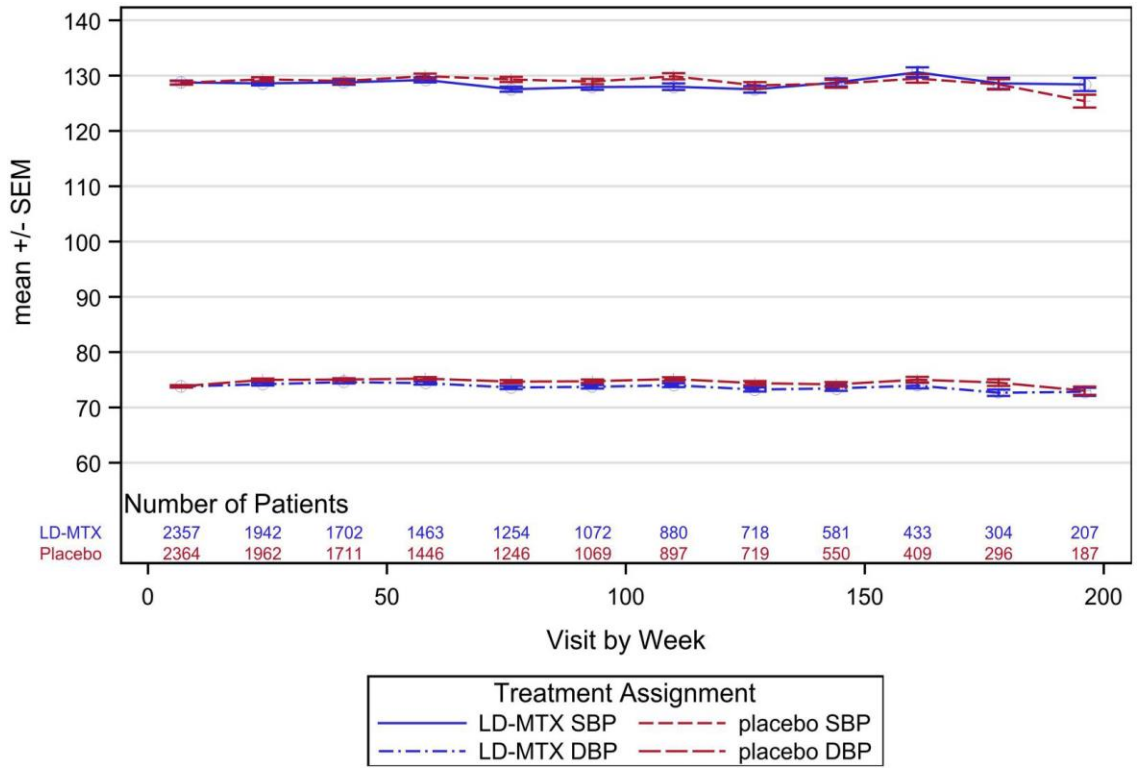
Roubille C, et al. Ann Rheum Dis 2015;74:480–489

Rheumatology, 2025, 00, 1–4
https://doi.org/10.1093/rheumatology/keae604
Advance access publication 6 December 2024
Concise report

British Society for Rheumatology RHEUMATOLOGY OXFORD

Clinical science

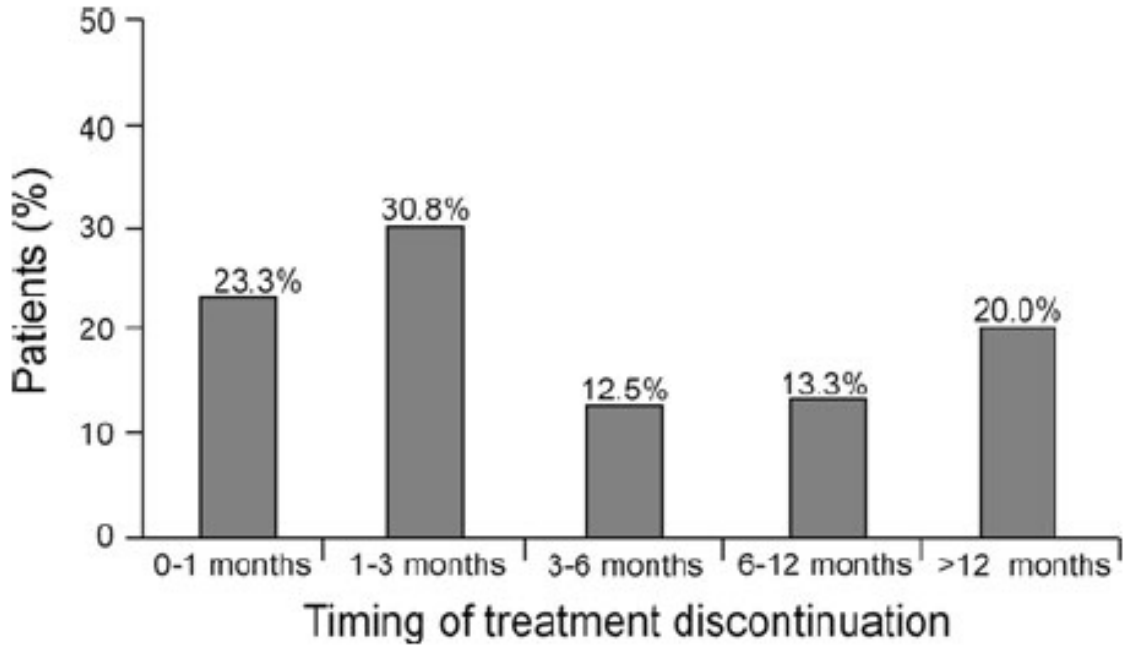
Blood pressure changes during methotrexate treatment: results from a randomized placebo-controlled trial among patients with cardiovascular risk



Rheumatology key messages

- **Evidence showed that immunosuppressive agent had a reduced risk of CVD events.**
- **Low-dose methotrexate is not effective at lowering blood pressure in patients without rheumatic disease.**
- **A major effect on blood pressure in patients treated with MTX for autoimmune diseases is unlikely.**

Γαστρική δυσανεξία σαν αίτιο διακοπής της MTX



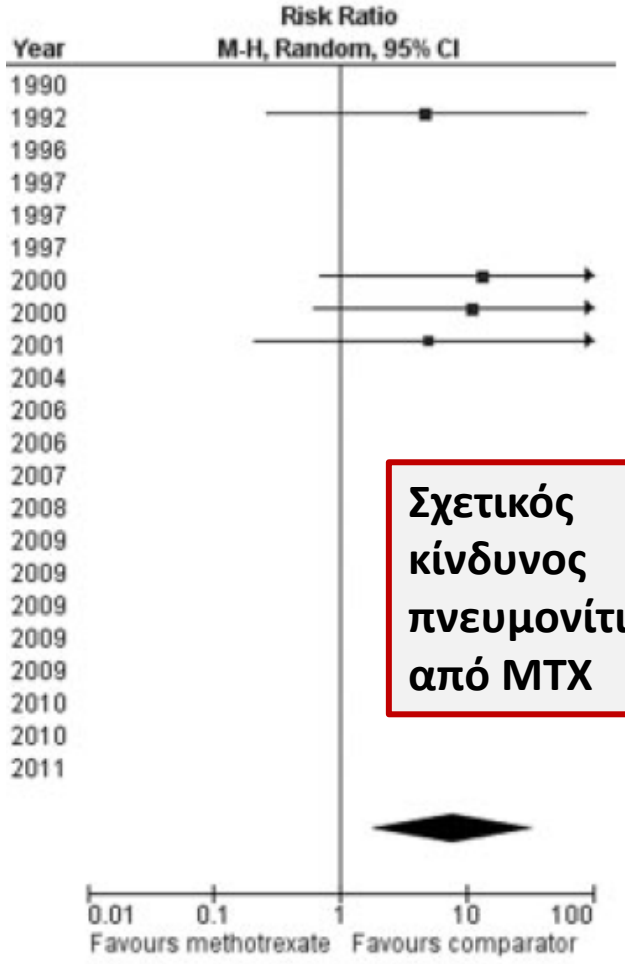
- **420 ασθενείς έλαβαν MTX per os για PA ή ΨΑ**
- **28.6 % διέκοψαν την αγωγή λόγω γαστρικής δυσανεξίας**
- **Ο μέσος χρόνος διακοπής της MTX λόγω της γαστρικής δυσανεξίας ήταν 8.1 ± 11.5 μήνες από την έναρξη, με την πλειονότητα το πρώτο τρίμηνο**
- **Ποσοστό 52.6 % των ασθενών που άλλαξε σε παρεντερική χορήγηση συνέχισε την θεραπεία**

Dalkilic E, Mod Rheumatol. 2013;23:525-8

Methotrexate and Lung Disease in Rheumatoid Arthritis

A Meta-Analysis of Randomized Controlled Trials

- **22 τυχαιοποιημένες μελέτες με 8.584 ασθενείς από το 1990 -2013**
- **Μελέτες >100 ασθενείς, >6 μήνες**
- **Αύξηση επεισοδίων αναπνευστικών λοιμώξεων (RR 1.11), όχι όμως μη λοιμωδών συμβάντων (RR 1.02)**
- **Στην υποομάδα των μελετών που καταγράφονται περιστατικά πνευμονίτιδας αναφέρεται RR 7.81**
- **Η πλέον πρόσφατη RCT που αναφέρει περιστατικό πνευμονίτιδας από μεθοτρεξάτη δημοσιεύθηκε το 2001**
- **Θεωρείται εξαιρετικά πιθανό ότι υπήρξε υπερεκτίμηση λόγω λανθασμένης διάγνωσης προ 20ετίας**



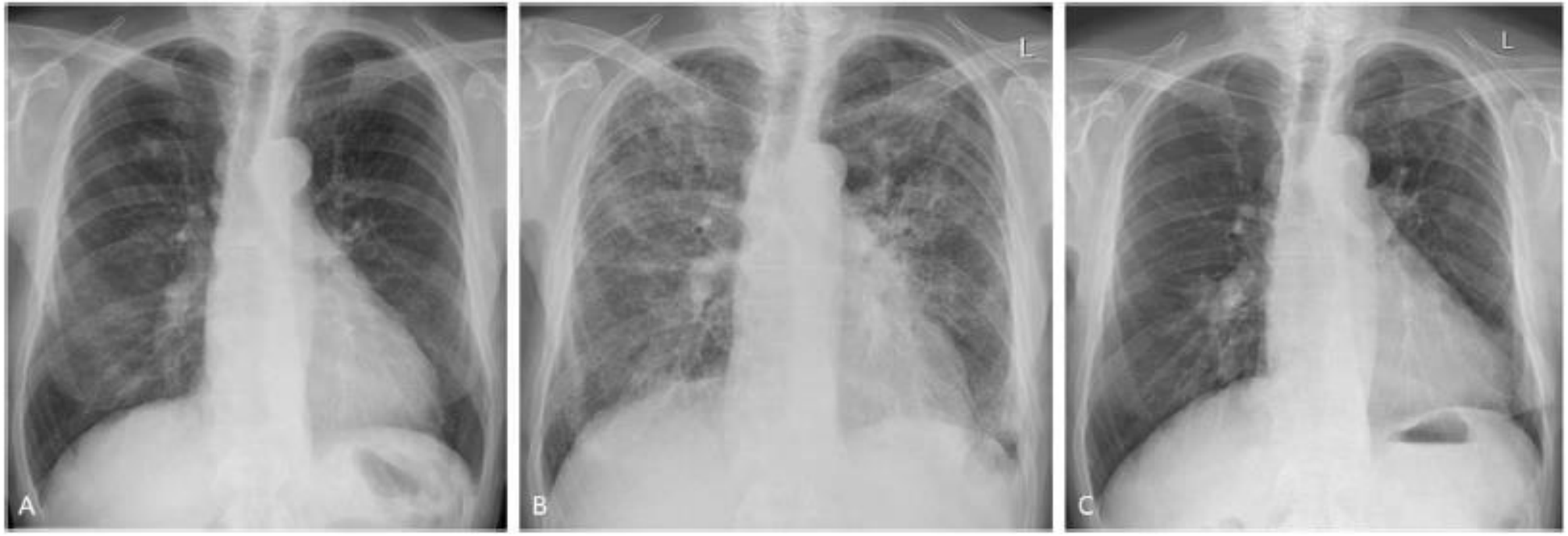
Σχετικός κίνδυνος πνευμονίτιδας από MTX

Conway R, Arthritis Rheum 2014; 66:803–812

Methotrexate-Associated Pneumonitis and Rheumatoid Arthritis-Interstitial Lung Disease: Current Concepts for the Diagnosis and Treatment

George E. Fragoulis [1,2], Elena Nikiphorou [3], Jörg Larsen [4], Peter Korsten [5] and Richard Conway [6]*

Οξεία πνευμονίτιδα από MTX



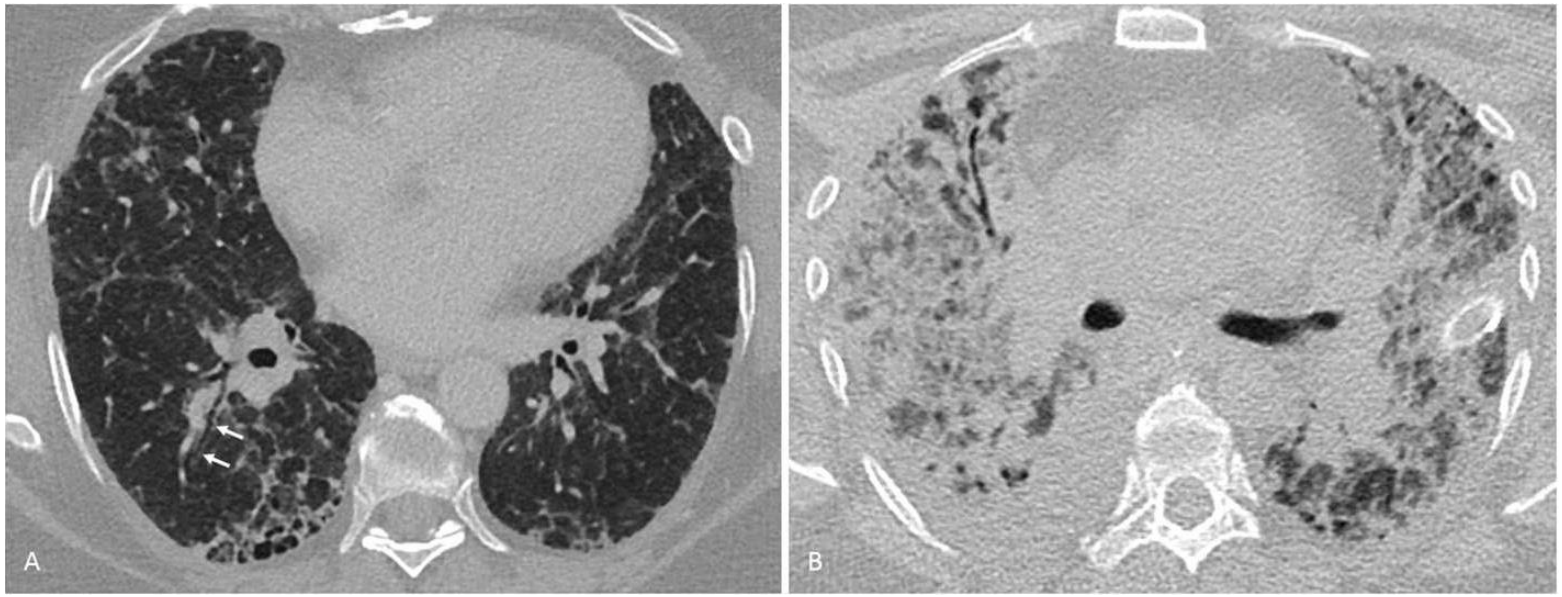
Methotrexate-induced pneumonitis in a 77-year-old man with rheumatoid arthritis. (A) Posterior-anterior chest radiograph immediately before the initiation of treatment. Following 10 days of methotrexate, the patient experienced progressive dyspnea and fever. Follow-up chest radiography showed bilateral heterogeneous opacities in all lung zones. (B) The patient was transferred to the intensive care unit for supportive treatment. High-dose glucocorticoids were administered and gradually withdrawn following clinical and radiological improvement. Initial high-resolution CT scanning showed diffuse infiltrates and bilateral patchy consolidations with only very limited ground-glass opacities (images not shown). (C) Seven months after stopping methotrexate, the changes of pulmonary toxicity had fully resolved

Fragoulis GE, Front Med (Lausanne). 2019 Oct 23;6:238

Methotrexate-Associated Pneumonitis and Rheumatoid Arthritis-Interstitial Lung Disease: Current Concepts for the Diagnosis and Treatment

*George E. Fragoulis[1,2], Elena Nikiphorou[3], Jörg Larsen[4], Peter Korsten[5] and Richard Conway[6]**

Ιογενής πνευμονίτιδα σε MTX



Interstitial lung disease in a 56-year-old woman with rheumatoid arthritis. (A) One millimeter transverse axial CT-section through the lung bases show subpleural honeycombing and early traction bronchiectasis (arrows), consistent with a usual interstitial pneumonia pattern. (B) Nine months later, the patient developed severe dyspnea at rest and required mechanical ventilation. On bronchoalveolar lavage, influenza A virus was found to be present. A follow-up CT now showed a small right-sided pleural effusion and multifocally confluent consolidation, partially obscuring equally patchy bilateral ground-glass opacification. A few thickened septae (crazy-paving pattern) could be delineated (not shown). These findings were consistent with a viral pneumonia. Despite extracorporeal membrane oxygenation therapy, the patient deceased.

Fragoulis GE, Front Med (Lausanne). 2019 Oct 23;6:238

Rheumatology, 2023, **62**, 2377–2385
https://doi.org/10.1093/rheumatology/keac651
Advance access publication 17 November 2022
Original article

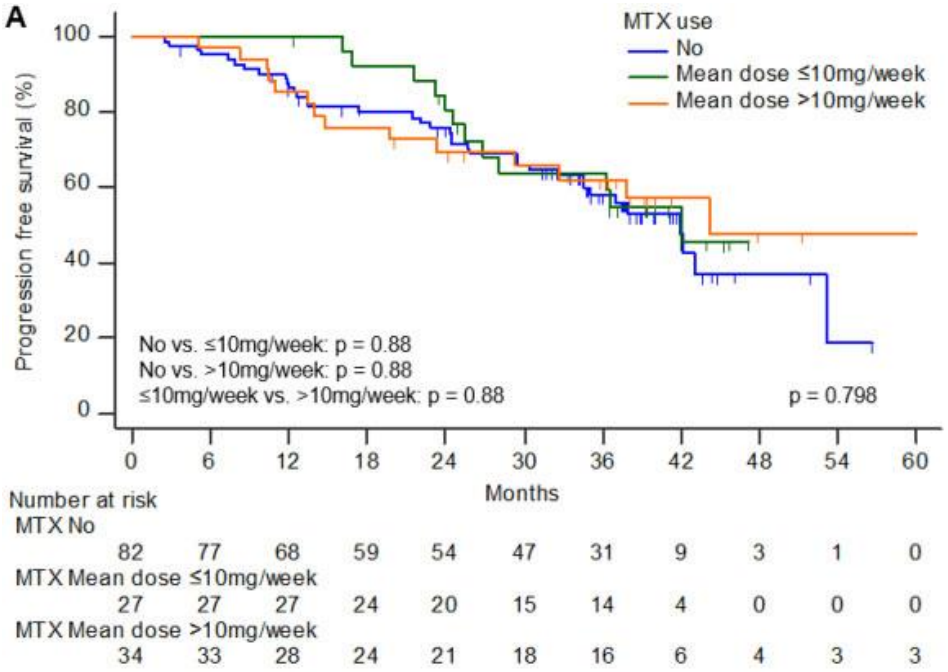
British Society for Rheumatology RHEUMATOLOGY OXFORD

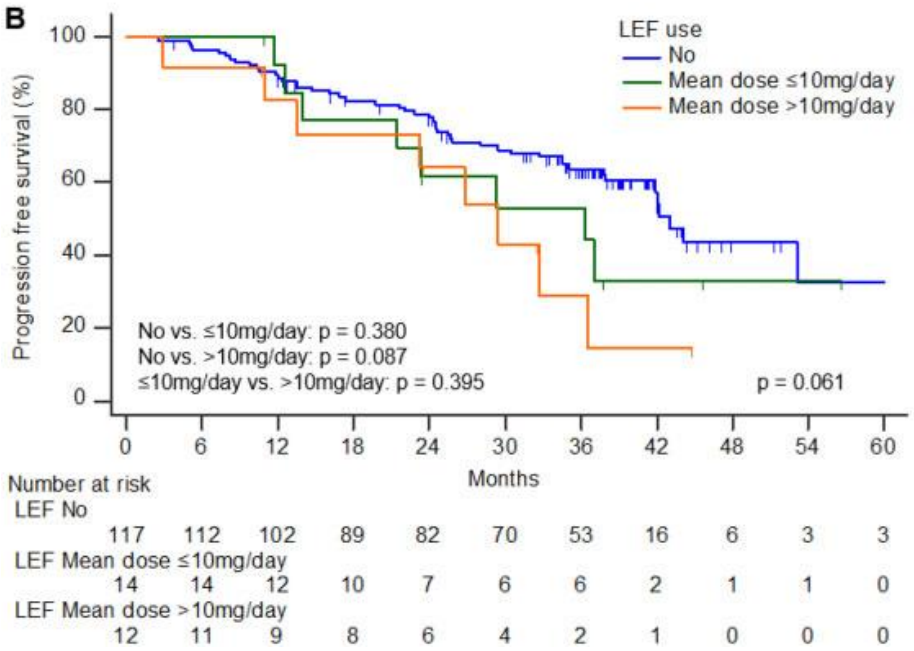
Clinical science

Methotrexate, leflunomide and tacrolimus use and the progression of rheumatoid arthritis-associated interstitial lung disease

Rheumatology key messages

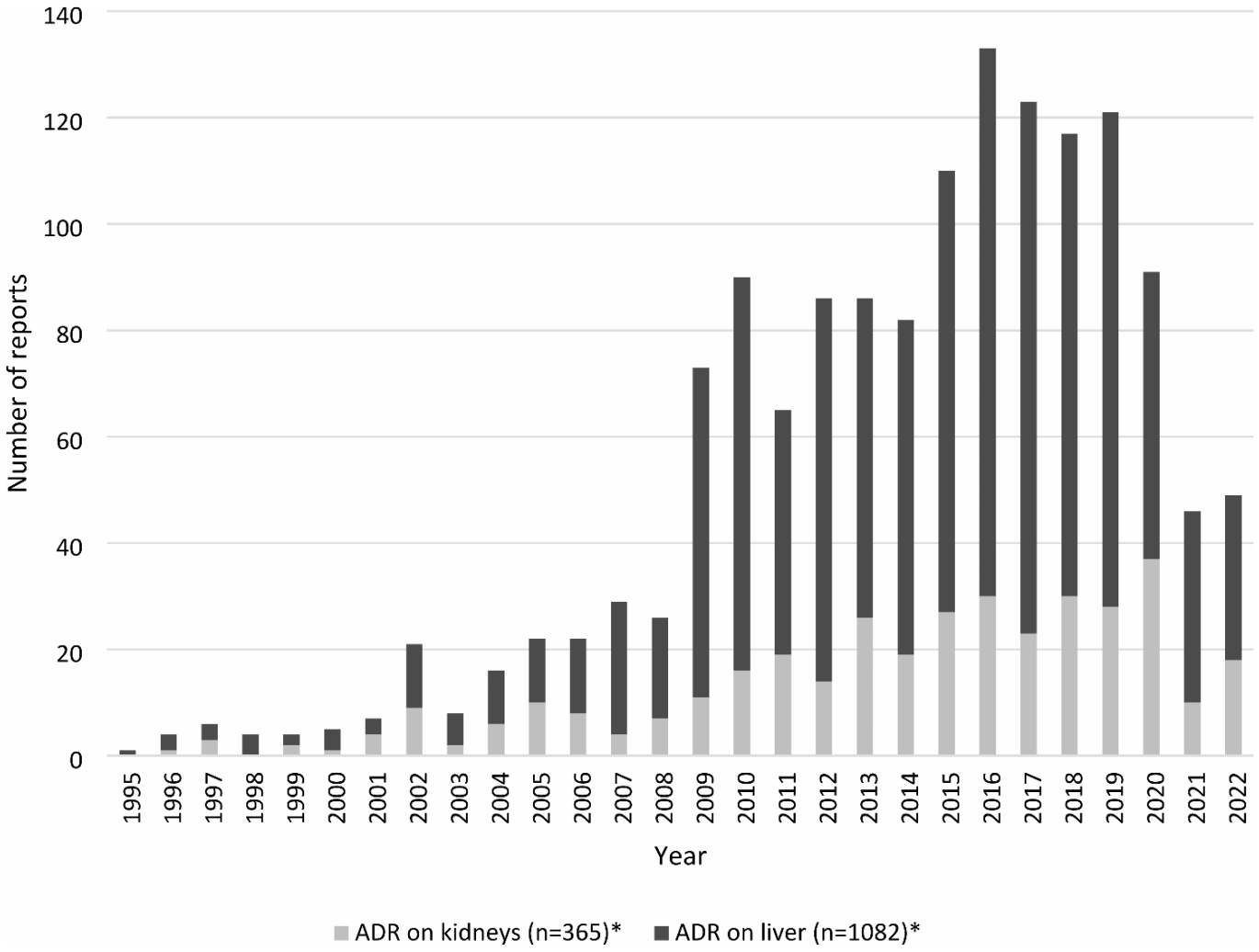
- Methotrexate, leflunomide and tacrolimus were not associated with the progression of rheumatoid arthritis (RA)-interstitial lung disease (ILD).
- The risk was significant when leflunomide was used in patients with severe ILD.
- Older age, male sex, shorter duration of RA, higher disease activity and extensive disease were independent risk factors for progression





Ji-Won Kim, Rheumatology, 2023, 62, 2377–2385

Methotrexate-related drug reactions on kidneys and liver in rheumatoid arthritis: an analysis of spontaneous reports in EudraVigilance



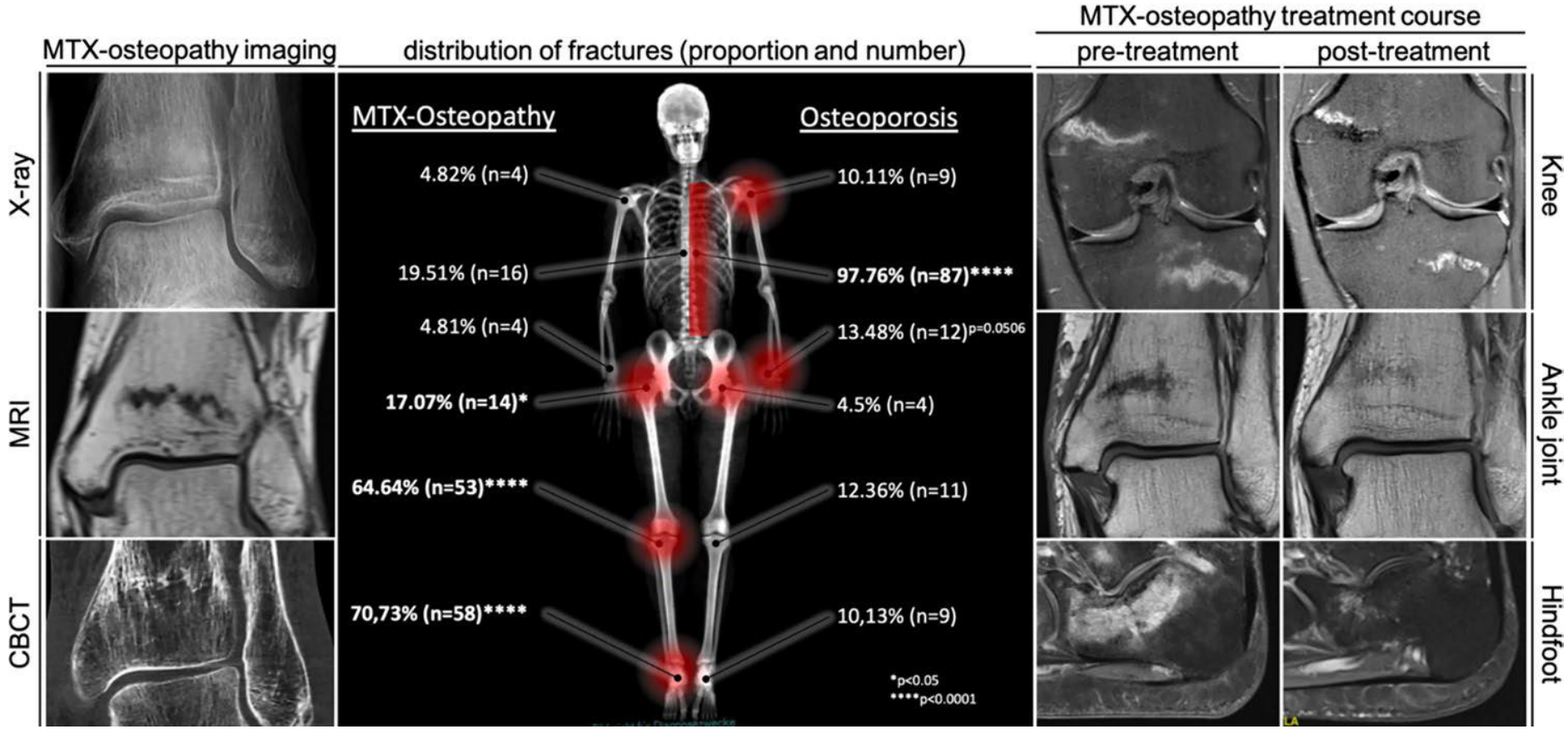
Patients with ADRs on the kidneys were older and comedication (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, metamizole and corticosteroids) was more common than in cases with ADRs on the liver. More patients with kidney- than liver-related ADRs had a fatal outcome (21.1% vs. 5.8%). In fatal cases with ADRs on the kidneys and with ADRs on the liver comedication was more common compared to non-fatal cases.

Khoroshun *et al. Arthritis Research & Therapy* (2025) 27:80

MTX Osteopathy Versus Osteoporosis Including Response to Treatment Data—A Retrospective Single Center Study Including 172 Patients

Οστεοπάθεια από μεθοτρεξάτη

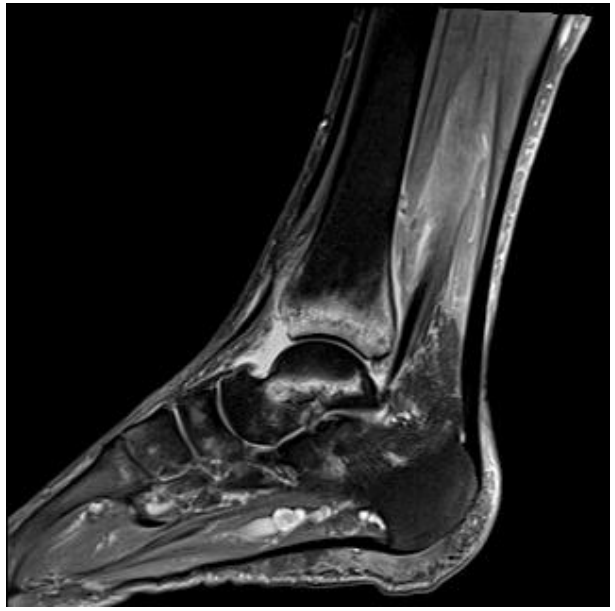
Felix N. von Brackel[1] · Jonathan Grambeck[1] · Florian Barvencik[1] · Michael Amling[1] · Ralf Oheim[1]

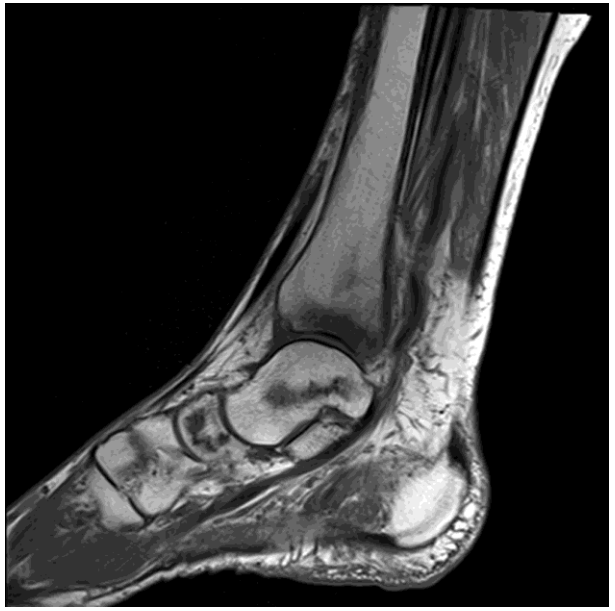


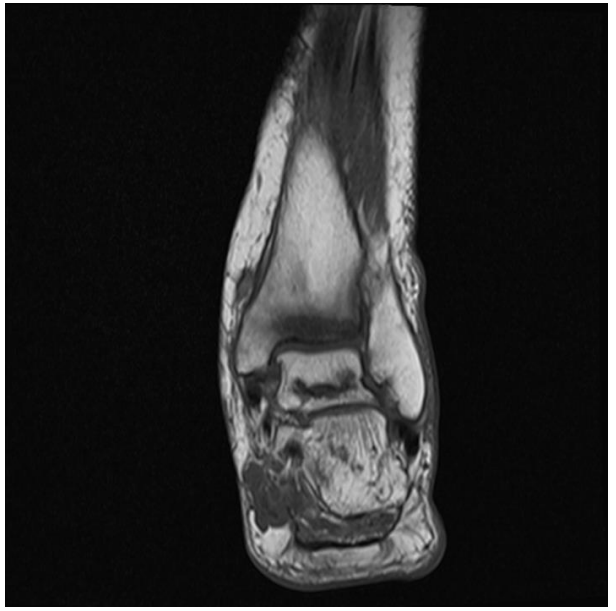
Calcified Tissue International (2024) 115:599–610

Οστεοπάθεια από μεθοτρεξάτη

Η οστεοπάθεια από μεθοτρεξάτη είναι μια σπάνια και υπομελετημένη οντότητα, που χαρακτηρίζεται από την τριάδα: οστεοπόρωση, άτυπα κατάγματα ανεπάρκειας κυρίως των κάτω άκρων και συνοδό άλγος μιμούμενο αρθρίτιδα







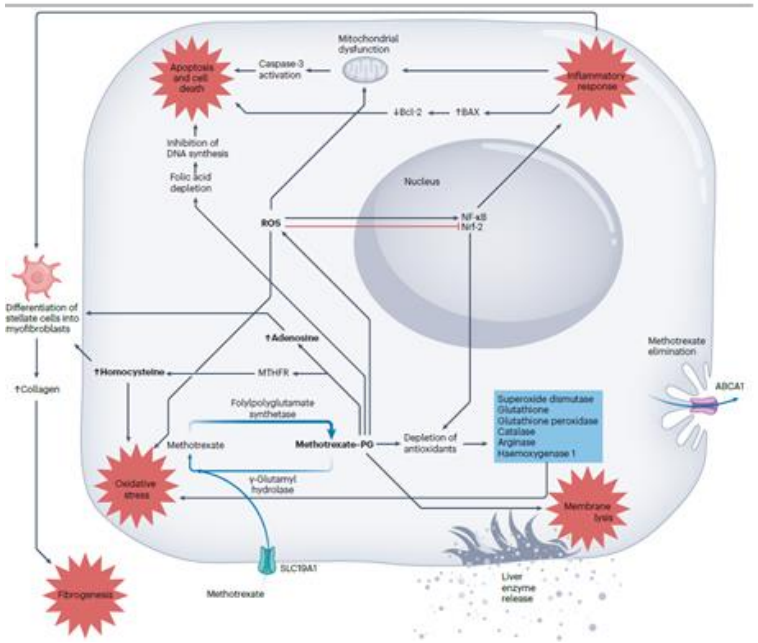
nature reviews rheumatology
https://doi.org/10.1038/s41584-022-00883-4

Review article

Check for updates

Busting the myth of methotrexate chronic hepatotoxicity

Patients with non-alcoholic fatty liver disease (NAFLD) are at increased risk for methotrexate hepatotoxicity, and methotrexate can worsen the course of NAFLD



Key points

- ••Methotrexate is a key component in the treatment of inflammatory rheumatic diseases and the mainstay of therapy in rheumatoid arthritis.
- ••In light of current evidence, it seems unlikely that methotrexate alone is capable of inducing chronic liver disease; the risk of methotrexate-induced liver injury is primarily acute in nature.
- ••The cumulative dose of methotrexate has no predictive value for the occurrence of fibrosis.
- ••In non-alcoholic fatty liver disease, several pathophysiological arguments suggest (in the absence of proof from clinical trials) that long-term methotrexate therapy worsens liver damage and the progression of liver disease.
- ••Pretreatment screening is advisable to check for the possible presence of liver disease in patients being considered for methotrexate treatment.
- ••Monthly monitoring is advocated at the beginning of methotrexate treatment, followed by 3-monthly monitoring comprising complete blood counts, liver function tests and calculation of the Fib-4 fibrosis score.

Di Martino V, Nat Rev Rheumatol. 2023;19(2):96-110

American College of Rheumatology
Empowering Rheumatology Professionals

Arthritis & Rheumatology
Vol. 74, No. 9, September 2022, pp 1464–1473
DOI 10.1002/art.42140

2022 American College of Rheumatology/American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Antirheumatic Medication in Patients With Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty

Πόσο διάστημα πρέπει να διακόπτουμε την ΜΤΧ για να γίνει αρθροπλαστική;

Recommendations

For patients with RA, AS, PsA, JIA, or all SLE undergoing elective THA or TKA, continuing the usual dosing of the following disease-modifying antirheumatic drugs (DMARDs) through surgery is conditionally recommended: methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, and/or apremilast.

Goodman SM, Arthritis Rheumatol. 2022 Sep;74(9):1464-1473

Arthritis & Rheumatology
Vol. 75, No. 3, March 2023, pp 333–348
DOI 10.1002/art.42386

American College of Rheumatology
Empowering Rheumatology Professionals

2022 American College of Rheumatology Guideline for Vaccinations in Patients With Rheumatic and Musculoskeletal Diseases

MTX και εμβόλια

Methotrexate

For patients with RMD, holding methotrexate for 2 weeks after influenza vaccination is conditionally recommended, assuming disease activity allows.

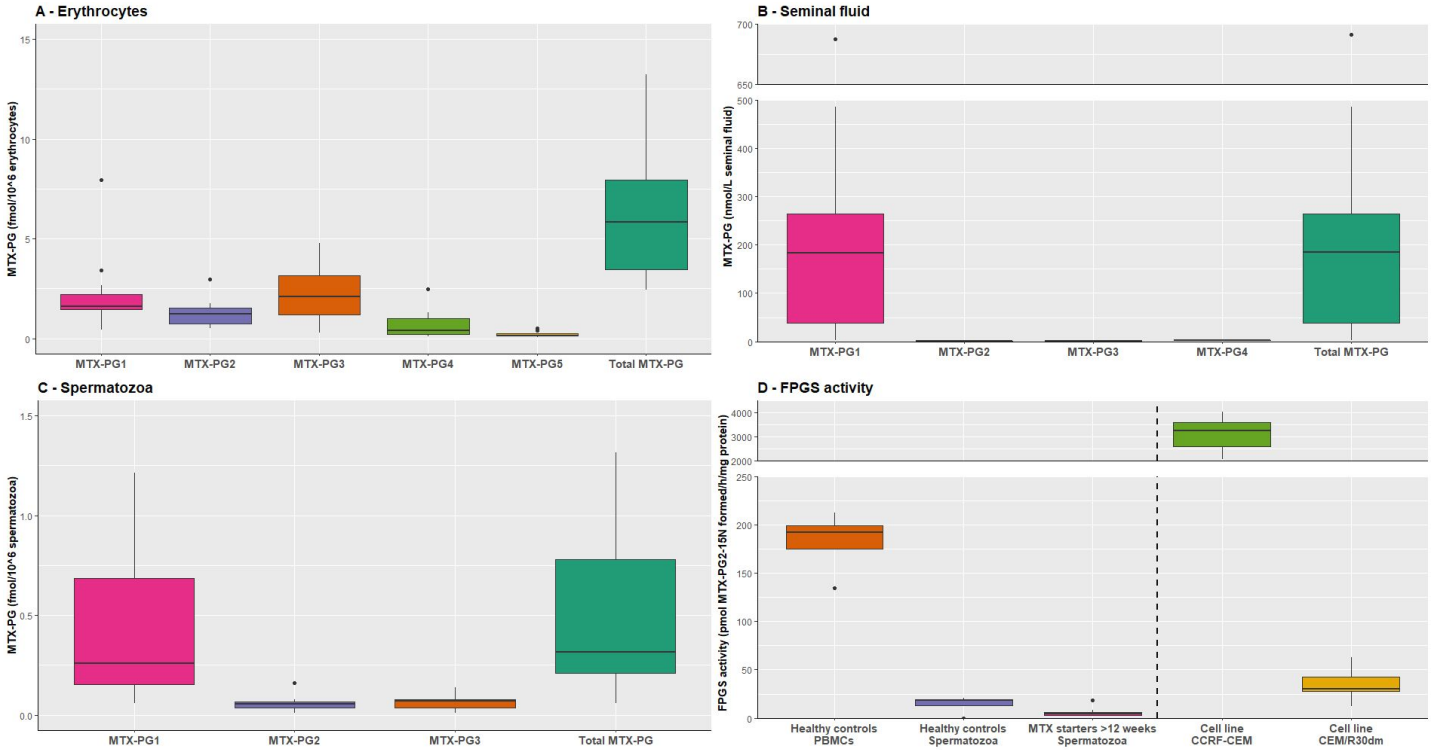
For patients with RMD, continuing immunosuppressive medications around the time of other (non-influenza) non–live attenuated vaccinations is conditionally recommended

For patients with RMD, holding immunosuppressivemedication for an appropriate period before and 4 weeks after live attenuated virus vaccination is conditionally recommended. (Όχι MTX 4 εβδομάδες πριν και μετά εμβόλια με ζώντες εξασθενημένους ιούς).

Bass AR, Arthritis Rheumatol. 2023 Mar;75(3):333-348

TRANSLATIONAL SCIENCE

Is methotrexate safe for men with an immune-mediated inflammatory disease and an active desire to become a father? Results of a prospective cohort study (iFAME-MTX)



MTX-polyglutamate (PG) accumulation in erythrocytes, seminal fluid and spermatozoa of RA patients and FPGS activity in spermatozoa

MTX σε άνδρες και τεκνοποίηση

Altogether, our data suggest that MTX is not associated with testicular toxicity. Therefore, therapy with MTX can be safely started or continued in men diagnosed with an IMID and with an active wish to become a father

Perez-Garcia LF, et al. Ann Rheum Dis 2023;82:1068–1075

Original Article

Recommendations for the Use of Parenteral Methotrexate in Rheumatic Diseases☆

Jesús Tornero Molina,[a,*] Jaime Calvo Alen,[b] Javier Ballina,[c] María Ángeles Belmonte,[d] Francisco J. Blanco,[e] Miguel Ángel Caracuel,[f] Jordi Carbonell,[g] Héctor Corominas,[h] Eugenio Chamizo,[i] Cristina Hidalgo,[j] José Román Ivorra,[k] José Luis Marenco,[l] José Vicente Moreno Muelas,[m] Santiago Muñoz-Fernández,[n] Joan M. Nolla,[o] Trinidad Pérez,[p] Raimon Sanmarti,[q] Pilar Trenor,[r] Claudia Urrego,[s] Javier Vidal,[a] José Rosas Gomez de Salazar[t]

Συστάσεις για την χρήση της παρεντερικής MTX

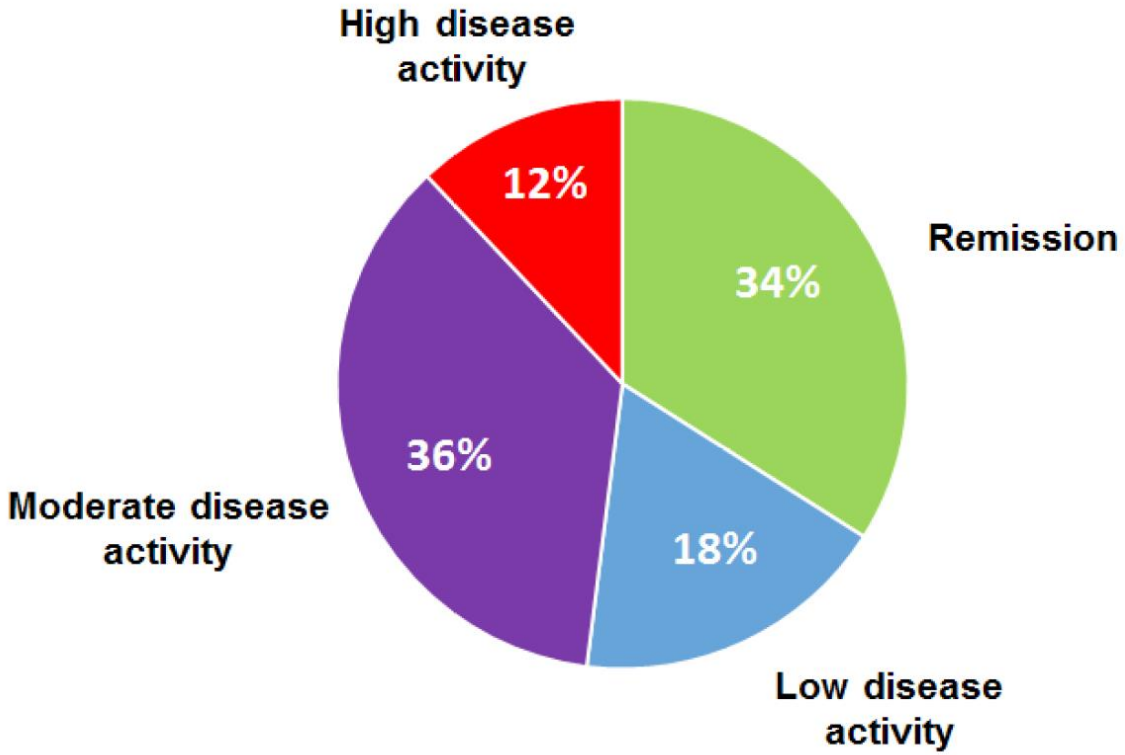
Number	Recommendation	LE; GR; LA
1	The bioavailability of parenteral MTX is superior to that of orally administered MTX, especially at doses ≥15 mg/week	LE 2b; GR B-C; LA 100%
2	In MTX-naive patients the clinical efficacy of parenteral MTX is superior to that delivered orally (at doses of 15 mg/week)	LE 1b; GR A; LA 94%
3	In patients with an inadequate response to oral MTX (15 mg/week), escalating the dose utilizing the parenteral route is clinically more effective	LE 2a; GR B; LA 94%
4	The safety and tolerability profile of MTX when delivered by the parenteral route is similar to that observed when it is administered orally	LE 1b; GR B; LA 100%
5	It is recommended that the use of parenteral MTX be considered in patients with highly active disease and in those who showed poor adherence to oral treatment, were taking multiple drugs or were obese, and to prevent dosing errors, always taking into account the preferences of the patient	LE 4; GR D; LA 100%
6	The recommendation is to follow the indications for the starting dose and increases and reductions applicable to the oral formulation	LE 5; GR D; LA 81%
7	The panel recommends a dose of up to 25–30 mg/week of parenteral MTX	LE 5; GR D; LA 88%
8	In accordance with the available pharmacokinetic data, the equivalences of the doses would be the same up to 15 mg; for 20 mg of oral MTX, the equivalent dose of parenteral MTX would be 15 mg and for 25 mg of oral MTX, 20 mg of parenteral MTX	LE 2b; GR B; LA 100%
9	Subcutaneous MTX can be cost-effective in early RA in MTX-naive patients	LE 2a; GR B; LA 94%
10	Parenteral administration can increase adherence to MTX	LE 2b; GR B; LA 94%
11	Education in self-administration results in a high rate of adherence to treatment, satisfaction, autonomy and favors correct administration	LE 2b; GR B; LA 100%

J. Tornero Molina et al, Reumatol Clin. 2018;14(3):142–149

MEDITERRANEAN JOURNAL OF RHEUMATOLOGY | 29 1 2018

ORIGINAL PAPER

Multicenter Cross-sectional Study of Patients with Rheumatoid Arthritis in Greece: Results from a cohort of 2.491 patients

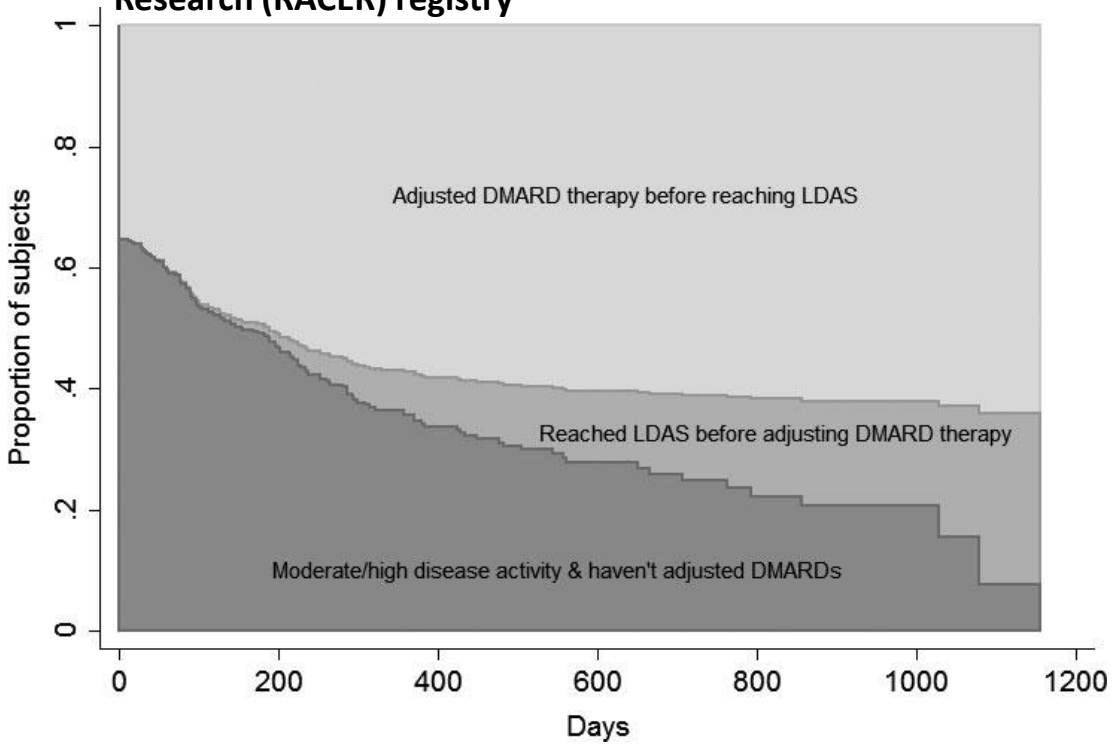


Current RA disease activity according to DAS28-ESR score. The current disease activity categories (%) of the RA cohort according to the Disease Activity Score 28 by the erythrocyte sedimentation rate (DAS28-ESR) is shown.

Thomas K, Mediterr J Rheumatol 2018; 29(1): 27-37

Timing and Impact of Decisions to Adjust Disease-Modifying Antirheumatic Drug Therapy for Rheumatoid Arthritis Patients With Active Disease

Data for years 2010–2013 of the University of Pittsburgh Rheumatoid Arthritis Comparative Effectiveness Research (RACER) registry



Status plot of subjects over time: by days since having moderate-to-high disease activity.

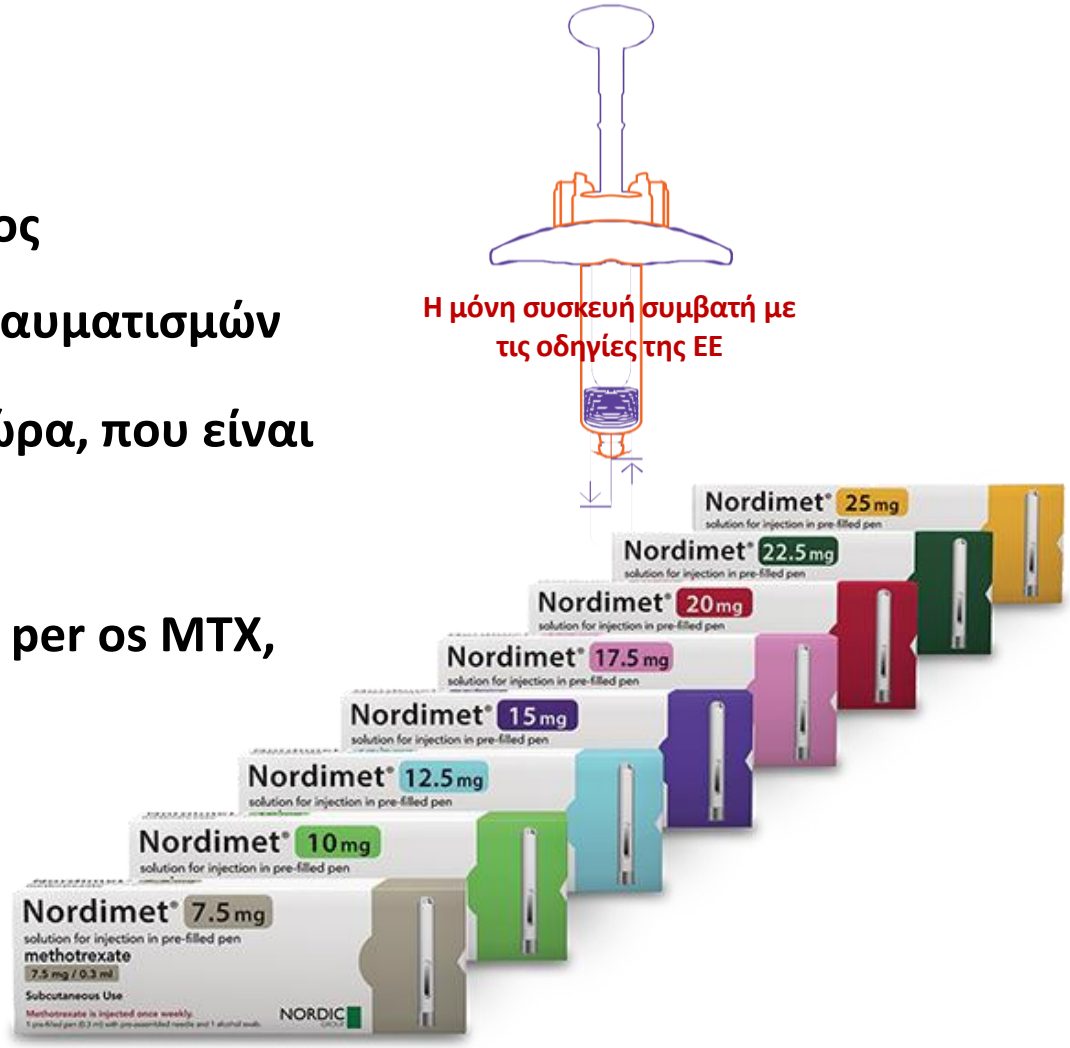
Προσαρμογή της θεραπείας στην PA και έκβαση

- **Forty percent of subjects with persistent MHDAS waited >90 days for DMARD therapy adjustment, suggesting that many RA patients may not be receiving timely therapy adjustment in clinical practice.**
- **Adjusting DMARDs within 90 days in response to MHDAS was associated with a higher likelihood of reaching LDAS during follow-up. This association indicates that attention to timing is important in implementing treat-to-target guidelines in RA.**

Shaw Y, Arthritis Care Res (Hoboken). 2018 Jun;70(6):834-841

Και το δορυφορικό σκέλος: Τι διαφορετικό έχει το υποδόριο Nordimet;

- **Λεπτή βελόνα 29G που δεν προκαλεί άλγος**
- **Αυτόματη ενεργοποίηση προστατευτικού κλειδώματος εισελκόμενης βελόνας για την αποφυγή ακούσιων τραυματισμών**
- **Αποφυγή δημιουργίας εκχυμώσεων στην κοιλιακή χώρα, που είναι σημαντικές κυρίως για νεαρά άτομα**
- **Διαθεσιμότητα ανά 2,5mg, όπως στην περίπτωση της per os MTX, δηλαδή σύριγγες των 10, 12.5, 15, 17.5, 20, 25mg**
- **Κάθε επιπλέον 2,5mg MTX, αντιστοιχούν σε 0,1 ml**



Συμπεράσματα

- Εβδομήντα έτη από τη σχεδίασή της και 35 από την εισαγωγή της στη θεραπεία της ΡΑ, δεν είναι επακριβώς γνωστός ο μηχανισμός δράσης της ΜΤΧ
- Δόσεις μεγαλύτερες των 15mg/εβδομάδα δεν έχουν πλήρη και γραμμική απορρόφηση από του στόματος, οπότε θα πρέπει να προτιμάται η υποδόρια χορήγηση
- Μέγιστη δόση της ΜΤΧ στην ΡΑ θεωρούνται τα 25mg την εβδομάδα
- Η υποδόρια χορήγηση πλεονεκτεί σε αποτελεσματικότητα και θα πρέπει πιθανώς να χορηγείται σε όλους τους ασθενείς πριν χορηγηθούν βιολογικοί παράγοντες λόγω ανεπαρκούς αποτελεσματικότητας

Recommendation

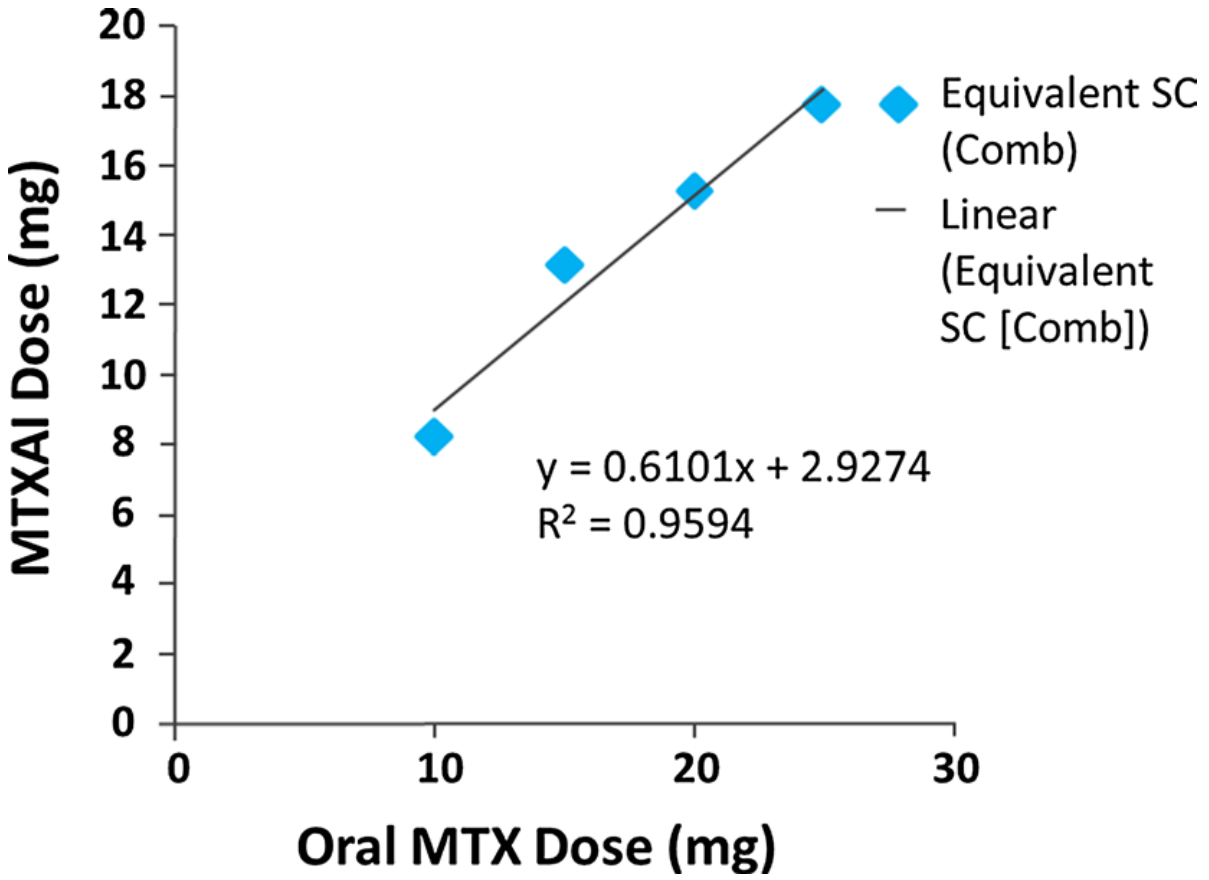
EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update

Μονοθεραπεία βιολογικών ή JAKi, ή συγχορήγηση με MTX;

9. *bDMARDs and tsDMARDs* should be combined with a csDMARD; in patients who cannot use csDMARDs as comedication, IL-6 pathway inhibitors and tsDMARDs* may have some advantages compared with other bDMARDs*... the EULAR Task Force continues to advocate the continuation of MTX (or other csDMARDs) when treatment with bDMARDs or JAKi is planned.

Smolen JS, Ann Rheum Dis 2023;82:3–18

Ισοδυναμία MTX από του στόματος και υποδορίως



Μετατροπή της MTX από του στόματος σε ισοδύναμη υποδόρια δόση

Schiff MH, Rheumatol Int 2017;37:213-218

Φαρμακευτικές αλληλεπιδράσεις της MTX

Interactions	Source of Interactions
Increase MTX levels	• Allopurinol, triamterene • Decrease renal MTX clearance: ciprofloxacin, cephalothin, penicillin, probenecid, sulfonamides • Decrease MTX excretion: diuretics, proton pump inhibitors • Increase MTX reabsorption by the kidney tubule: probenecid
Decrease MTX levels	• Decrease intestinal absorption of MTX: chloramphenicol, tetracyclines
Increase the risk of bone marrow suppression	• Chloramphenicol, co-trimoxazole, pyrimethamine, sulfonamides, trimethoprine-sulfamethoxazole
Increase liver toxicity	• Alcohol, leflunomide

Taylor PC, J Clin Med. 2019;8(4):515

Identification of Risk Factors for Elevated Transaminases in Methotrexate Users Through an Electronic Health Record

Προγνωστικοί παράγοντες για αύξηση των τρανσαμινασών λόγω λήψης MTX:

- **Παχυσαρκία (body mass index >30 kg/m^2)**
- **Χοληστερόλη >240 mg/dl**
- **Αύξηση των τρανσαμινασών πριν τη χορήγηση MTX**
- **Συγχορήγηση βιολογικών παραγόντων**
- **Μη ταυτόχρονη χορήγηση φολικού οξέος**

Ασθενής με αυτά τα χαρακτηριστικά και >3 παράγοντες συννοσηρότητας προβλέπεται να έχει 90% πιθανότητα αύξησης των τρανσαμινασών τους πρώτους 7 μήνες από την έναρξη αγωγής με MTX

Schmajuk G et al, Arthritis Care Res 2014; 66: 1159–1166