DMARDs

Τί συστήνουν οι κατευθυντήριες οδηγίες;

Χρήστος Γκαμαλούτσος
Ρευματολόγος

Σύγκρουση συμφερόντων
Conflict of interest

Κανένα για αυτήν την παρουσίαση

Εκπαιδευτικές-ερευνητικές-συμβουλευτικές επιχορηγήσεις την τελευταία διετία:

UCB, Roche

eular

ΕΛΛΗΝΙΚΗ ΡΕΥΜΑΤΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ
& ΕΠΑΓΓΕΛΜΑΤΙΚΗ ΕΝΩΣΗ ΡΕΥΜΑΤΟΛΟΓΩΝ ΕΛΛΑΔΟΣ

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

ΕΛΛΗΝΙΚΟ ΑΡΧΕΙΟ ΒΙΟΛΟΓΙΚΩΝ ΘΕΡΑΠΕΙΩΝ · 2004 · HELLENIC REGISTRY FOR BIOLOGIC THERAPIES · 2004 ·

THE BRITISH SOCIETY FOR RHEUMATOLOGY
BSR
BHPR
British Health Professionals in Rheumatology

Κριτήρια κατάταξης φαρμάκων ως τροποποιητικά (DMARDs)

1. Βραδεία έναρξη δράσης
2. Επίδραση στην αντίδραση οξείας φάσης
3. Βελτίωση της λειτουργικής κατάστασης
4. Επιβράδυνση της εξέλιξης των ακτινολογικών βλαβών

Sturrock RD. in Rheumatology 4th ed. M Hochberg editor

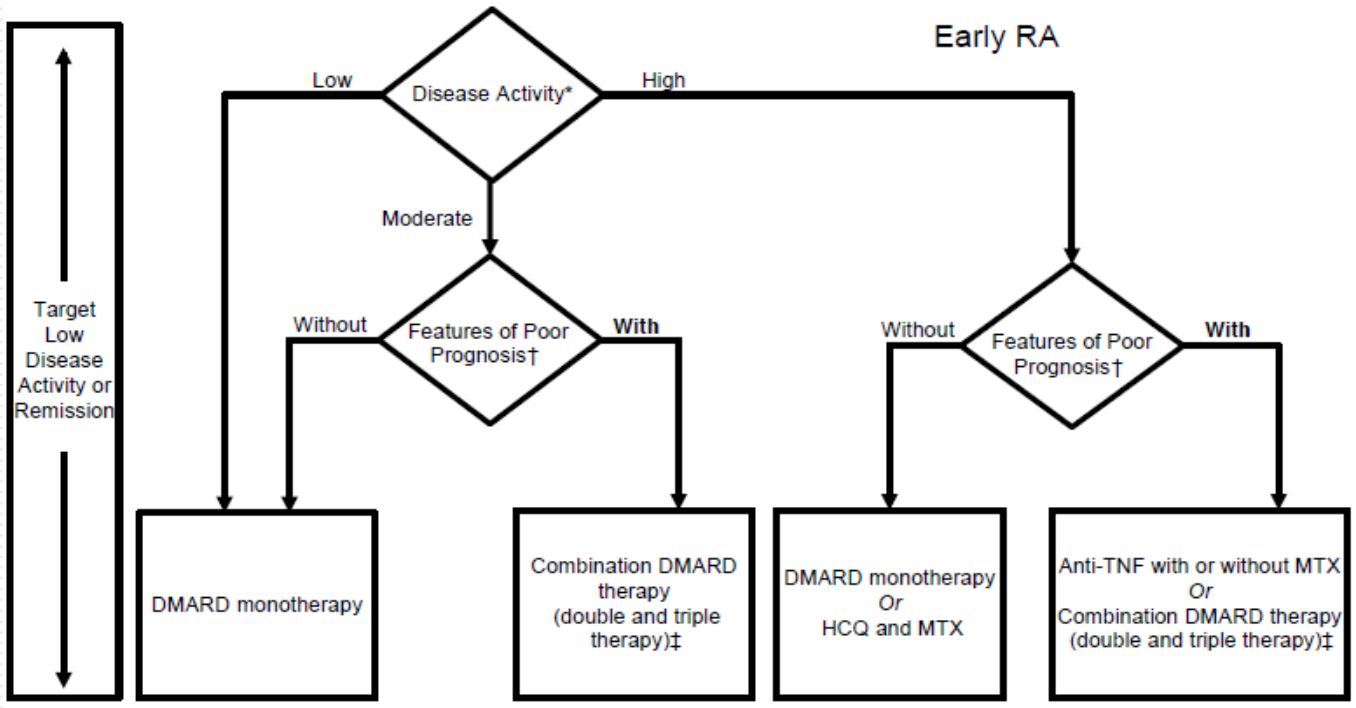
Ι. ΣΥΣΤΑΣΕΙΣ ΓΙΑ ΤΗ ΧΡΗΣΗ ΤΩΝ DMARDs ΣΤΗ ΡΑ

Γενικές αρχές θεραπευτικής

- Η θεραπεία με DMARDs πρέπει να αρχίζει το συντομότερο (με τη διάγνωση της νόσου)
- Στόχος της θεραπείας είναι η ύφεση ή η χαμηλή ενεργότητα της νόσου
- Η αγωγή πρέπει να αξιολογείται συχνά και να τροποποιείται αν ο στόχος δεν επιτυγχάνεται

2012 ACR recommendations update for the treatment of early RA, defined as a disease duration <6 months.

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

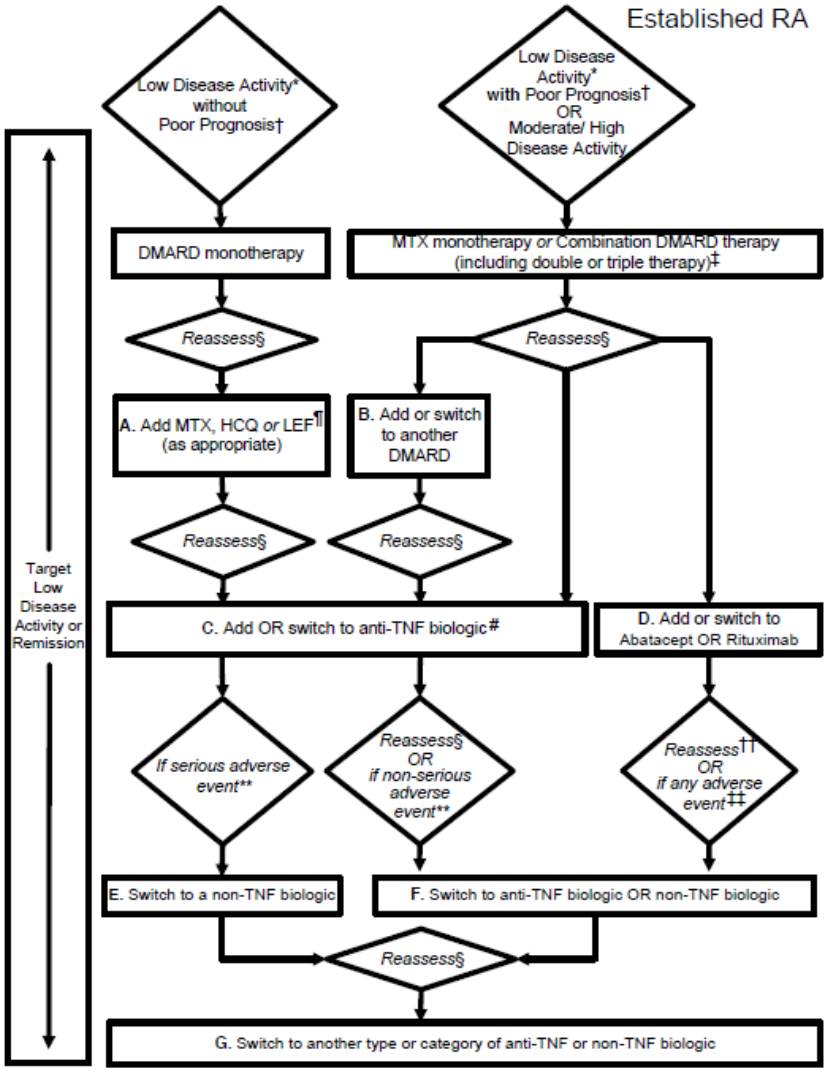


DMARDs

- LEF
- MTX
- SSZ
- HCQ
- MIN

Singh et al, Arthritis Care & Research 2012

2012 ACR recommendations update for the treatment of established RA, defined as a disease duration >6 months or meeting the 1987 ACR classification criteria.



AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

DMARDs

- LEF
- MTX
- SSZ
- HCQ
- MIN

Singh et al, Arthritis Care & Research 2012

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

3	MTX should be part of the first treatment strategy in patients with active RA
4	When MTX contraindications (or intolerance) are present, the following DMARDs should be considered as part of the (first) treatment strategy: leflunomide, SSZ or injectable gold
5	In DMARD naïve patients, irrespective of the addition of GCs, synthetic DMARD monotherapy rather than combination therapy of synthetic DMARDs may be applied
6	GCs added at low to moderately high doses to synthetic DMARD monotherapy (or combinations of synthetic DMARDs) provide benefit as initial short-term treatment, but should be tapered as rapidly as clinically feasible

eular

Smolen JS, Landewé R, Breedveld FC, *et al*. *Ann Rheum Dis* (2010)

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

10	In cases of refractory severe RA or contraindications to biological agents or the previously mentioned synthetic DMARDs, the following synthetic DMARDs might be also considered, as monotherapy or in combination with some of the above: azathioprine, ciclosporin A (or exceptionally, cyclophosphamide)
11	Intensive medication strategies should be considered in every patient, although patients with poor prognostic factors have more to gain

eular

Smolen JS, Landewé R, Breedveld FC, *et al*. *Ann Rheum Dis* (2010)

ΕΛΛΗΝΙΚΟ ΑΡΧΕΙΟ ΒΙΟΛΟΓΙΚΩΝ ΘΕΡΑΠΕΙΩΝ ΕΠΙΚΑΙΡΟΠΟΙΗΣΗ ΤΩΝ ΣΥΣΤΑΣΕΩΝ ΓΙΑ ΤΗ ΧΡΗΣΗ ΤΩΝ ΒΙΟΛΟΓΙΚΩΝ ΠΑΡΑΓΟΝΤΩΝ ΣΤΗ ΡΕΥΜΑΤΟΕΙΔΗ ΑΡΘΡΙΤΙΔΑ ΚΑΙ ΤΙΣ ΣΠΟΝΔΥΛΑΡΘΡΙΤΙΔΕΣ (2012)

5. Η μεθοτρεξάτη ή η λεφλουνομίδη θα πρέπει να έχει οπωσδήποτε χρησιμοποιηθεί, εκτός και αν υπάρχουν αντενδείξεις για τη χορήγησή τους.

6. Επαρκής θεραπευτική δοκιμή των DMARDs θεωρείται θεραπεία διάρκειας τουλάχιστον 3 μηνών στις παρακάτω δόσεις - στόχους:

Μεθοτρεξάτη: ≥15 mg/ εβδομάδα, με δόση στόχο 20-25mg/w, εφόσον είναι ανεκτό
Λεφλουνομίδη: 20 mg/ημέρα
Σουλφασαλαζίνη: 3 gr/ημέρα
Υδροξυχλωροκίνη: 400 mg/ημέρα
Κυκλοσπορίνη: 3 mg/kg/ημέρα

7. Ασθενείς με **πρώιμη ρευματοειδή αρθρίτιδα** (διάρκεια συμπτωμάτων < 12 μήνες)οι οποίοι θα ξεκινήσουν για πρώτη φορά αγωγή συνιστάται να λάβουν κλασσικά DMARDs (μεθοτρεξάτη, λεφλουνομίδη, σουλφασαλαζίνη, υδροξυχλωροκίνη, κυκλοσπορίνη).

ΘΕΡΑΠΕΥΤΙΚΑ ΠΡΩΤΟΚΟΛΛΑ ΣΥΝΤΑΓΟΓΡΑΦΗΣΗΣ ΡΕΥΜΑΤΟΛΟΓΙΚΩΝ ΝΟΣΗΜΑΤΩΝ 2011- (PA)

- **1ης Επιλογή**
  - Γλυκοκορτικοειδή 7.5mg/ημέρα
  +
  - Μεθοτρεξάτη (7.5 – 20 mg εβδομαδιαίως, μέγιστη δόση 25 mg) και φυλλικό οξύ (5mg/εβδομάδα)

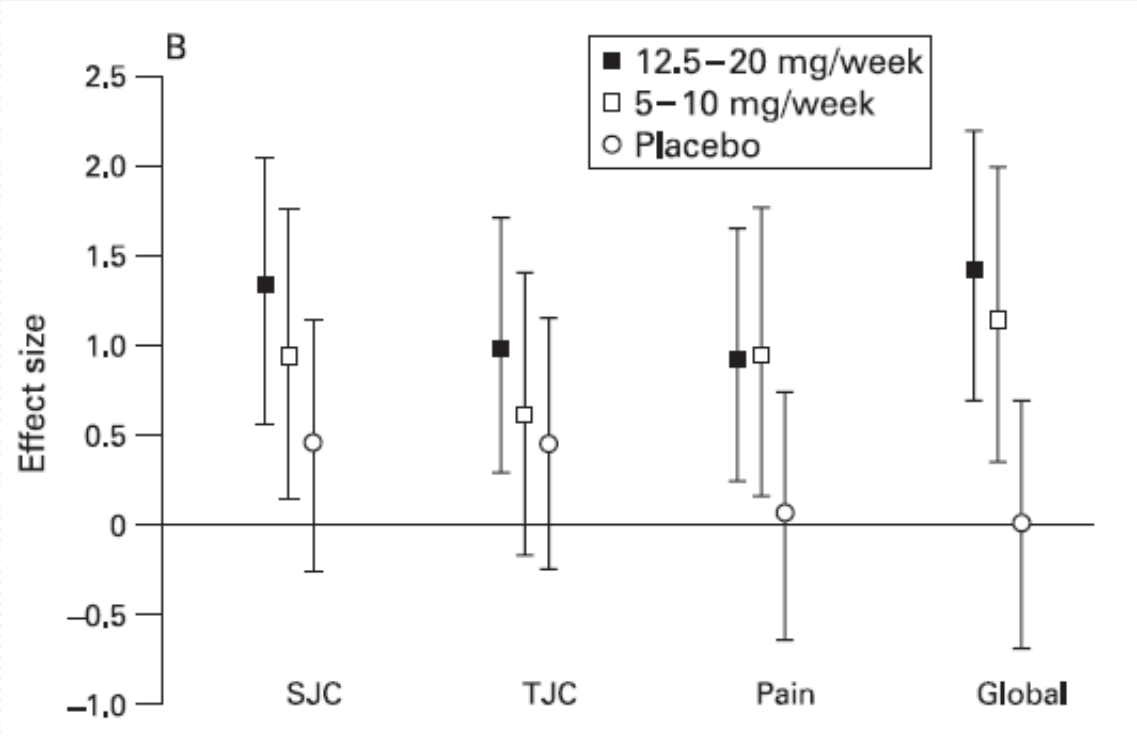
- Σε περίπτωση δυσανεξίας στην μεθοτρεξάτη μπορούν να χρησιμοποιηθούν τα ακόλουθα:
  - λεφλουνομίδη,
  - **κυκλοσπορίνη,**
  - σουλφασαλαζίνη,
  - **ενέσιμος χρυσός**,
  - υδροξυχλωροκίνη,ή/και συνδυασμοί τους

Ποιο DMARD είναι η πρώτη επιλογή;

- Η ΜΤΧ, είναι η πρώτη επιλογή σύμφωνα με τις περισσότερες συστάσεις

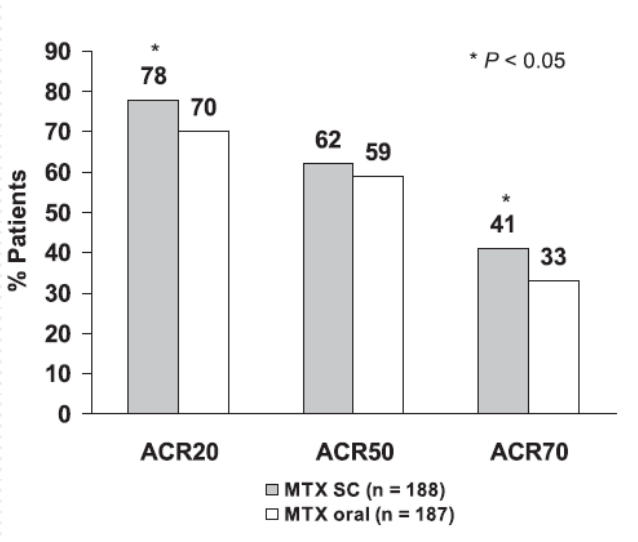
- Η αποτελεσματικότητά της αυξάνει
  - με χορήγηση τουλάχιστον 10mg/wk αρχικά
  - με την γρήγορη αύξηση της δόσης
  - σε υψηλότερες δόσεις **20-30 mg/wk**
  - κατά την **υποδόρια** χορήγησή της

η MTX είναι αποτελεσματικότερη σε μεγαλύτερες δόσεις

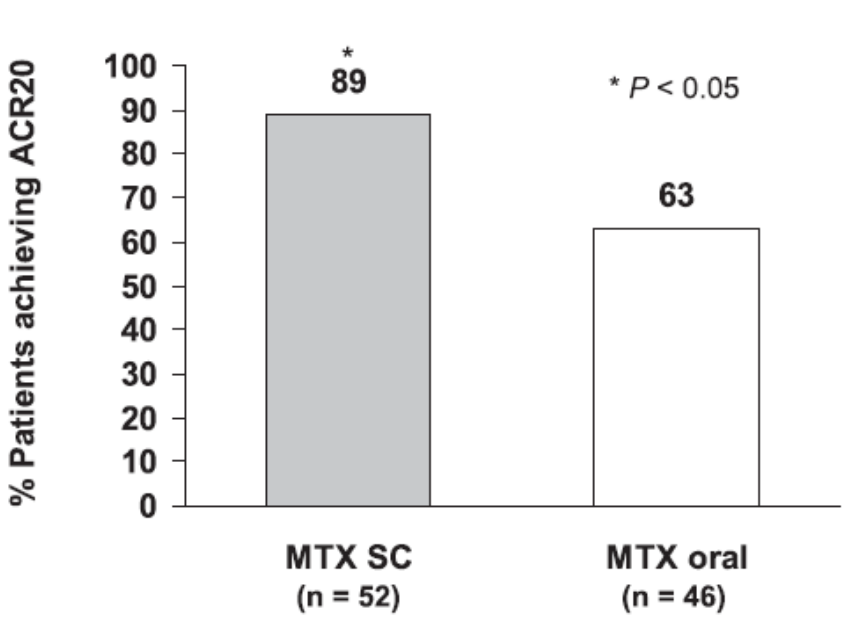


Visser et al, Ann Rheum Dis 2009;68:1094–1099.

η MTX είναι αποτελεσματικότερη χορηγούμενη υποδόρια



Percentages of patients achieving a response according to the American College of Rheumatology criteria for 20% improvement (ACR20), 50% improvement (ACR50), and 70% improvement (ACR70) at week 24 (full analysis set). The ACR20 and ACR70 responses in patients taking subcutaneous (SC)methotrexate (MTX) were significantly different from those in patients taking oral MTX.



Percentages of patients with a time between diagnosis and study entry of 1 year who achieved a response according to the American College of Rheumatology criteria for 20% improvement (ACR20) at week 24 (full analysis set).

BRAUN ET AL, ARTHRITIS & RHEUMATISM 2008

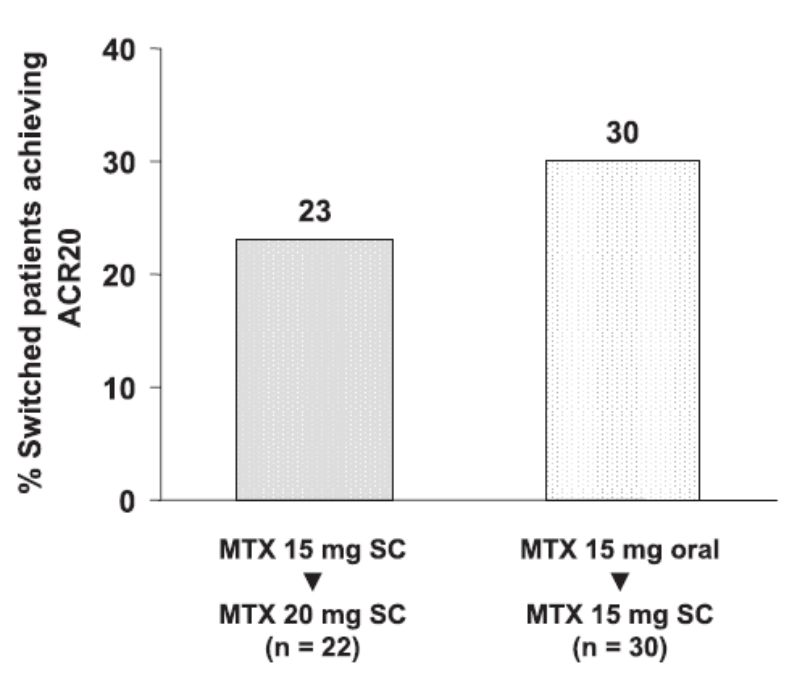
Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on RA: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative

Table 2 Multinational recommendations for the use of methotrexate in RA (1–7, 9–10) and other rheumatic disorders (8)

	Recommendation	Level of evidence	Grade of recommendation	Agreement mean (SD)
1	The work-up for patients starting methotrexate should include clinical assessment of risk factors for methotrexate toxicity (including alcohol intake), patient education, AST, ALT, albumin, CBC, creatinine, chest *x* ray (obtained within the previous year); consider serology for HIV, hepatitis B/C, blood fasting glucose, lipid profile and pregnancy test.	4	C	8.2 (1.9)
2	Oral methotrexate should be started at 10–15 mg/week, with escalation of 5 mg every 2–4 weeks up to 20–30 mg/week, depending on clinical response and tolerability; parenteral administration should be considered in the case of inadequate clinical response or intolerance.	2b	B	7.8 (2.6)
3	Prescription of at least 5 mg folic acid per week with methotrexate therapy is strongly recommended.	1a–	A	7.5 (2.7)
4	When starting methotrexate or increasing the dose, ALT with or without AST, creatinine and CBC should be performed every 1–1.5 months until a stable dose is reached and every 1–3 months thereafter; clinical assessment for side effects and risk factors should be performed at each visit.	4	C	8.1 (2.1)
5	Methotrexate should be stopped if there is a confirmed increase in ALT/AST greater than three times the ULN, but may be reinstituted at a lower dose following normalisation. If the ALT/AST levels are persistently elevated up to three times the ULN, the dose of methotrexate should be adjusted; diagnostic procedures should be considered in the case of persistently elevated ALT/AST more than three times the ULN after discontinuation.	2b	C	7.4 (2.3)
6	Based on its acceptable safety profile, methotrexate is appropriate for long-term use.	2b	B	8.7 (1.9)
7	In DMARD-naive patients the balance of the efficacy/toxicity favours methotrexate monotherapy over combination with other conventional DMARD; methotrexate should be considered as the anchor for combination therapy when methotrexate monotherapy does not achieve disease control.	1a–	A	8.3 (2.1)
8	Methotrexate, as a steroid-sparing agent, is recommended in giant-cell arteritis and polymyalgia rheumatica and can be considered in patients with systemic lupus erythematosus or (juvenile) dermatomyositis.	1b	B	7.7 (2.1)
9	Methotrexate can be safely continued in the perioperative period in RA patients undergoing elective orthopaedic surgery.	1b	B	8.8 (1.9)
10	Methotrexate should not be used for at least 3 months before planned pregnancy for men and women and should not be used during pregnancy or breast feeding.	4	C	8.2 (2.7)

Visser et al, Ann Rheum Dis 2009;68:1086–1093

Per os vs sc MTX



Percentages of patients achieving a response according to the American College of Rheumatology criteria for 20% improvement (ACR20) at week 24 who had been ACR20 nonresponders at week 16.Patients who did not meet the ACR20 criteria at week 16 were switched from 15 mg of oral methotrexate (MTX) to 15 mg of subcutaneous (SC) MTX and from 15 mg of SC MTX to 20 mg of SC MTX for the remaining 8 weeks of study (full analysis set)

BRAUN ET AL, ARTHRITIS & RHEUMATISM 2008

Μηνύματα από τις συστάσεις

- Χορήγηση υψηλής δόσης MTX >20mg / wk
- τα γλυκοκορτικοειδή ως DMARDs
- Ο **ενδομυϊκός χρυσός** περιλαμβάνεται στις συστάσεις των EULAR, EPE
- Η **κυκλοσπορίνη** είναι μεταξύ των DMARDs που περιλαμβάνονται στις οδηγίες των: EULAR, EPE, ΕΛΛΗΝΙΚΟΥ ΑΡΧΕΙΟΥ ΒΙΟΛΟΓΙΚΩΝ ΘΕΡΑΠΕΙΩΝ

ΙΙ. ΣΥΣΤΑΣΕΙΣ ΓΙΑ ΤΗ ΧΡΗΣΗ ΤΩΝ DMARDs ΣΕ ΑΛΛΑ ΡΕΥΜΑΤΙΚΑ ΝΟΣΗΜΑΤΑ (ΕΝΔΕΙΚΤΙΚΗ ΚΑΤΑΓΡΑΦΗ)

	ΕΛΛΗΝΙΚΗ ΡΕΥΜΑΤΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ & ΕΠΑΓΓΕΛΜΑΤΙΚΗ ΕΝΩΣΗ ΡΕΥΜΑΤΟΛΟΓΩΝ ΕΛΛΑΔΟΣ ΕΟΘ	eular
Νόσος Still ενηλίκων	MTX, LEF, CSA, AZA	
Αγκυλωτική σπονδυλίτιδα	MTX, SSZ	SSZ
Ψωριασική αρθρίτιδα	MTX, CSA, LEF, SSZ	MTX, SSZ,LEF, CSA
Εντεροπαθητική αρθρίτιδα	SSZ	
ΣΕΛ	HCQ, MTX, CSA, AZA	HCQ, AZA
ΣΕΛ-νεφρική προσβολή	CYC, AZA, MMF	CYC, AZA, MMF, CSA, HCQ
Sjogren	HCQ, MTX, CYC, AZA	
Behcet's	AZA, CSA	AZA, CSA, CYC,CSA SSZ, THA MTX

ΙΙΙ. ΣΥΣΤΑΣΕΙΣ ΣΧΕΤΙΚΑ ΜΕ ΤΗΝ ΑΣΦΑΛΕΙΑ ΤΩΝ DMARDs

Συστάσεις εμβολιασμού πριν και κατά τη διάρκεια της αγωγής με DMARDs

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

Table 5. 2012 American College of Rheumatology recommendations update regarding the use of vaccines in patients with RA starting or currently receiving DMARDs or biologic agents*

	Killed vaccines			Recombinant vaccine	Live attenuated vaccine
	Pneumococcal†	Influenza (intramuscular)	Hepatitis B‡	Human papillomavirus	Herpes zoster
Before initiating therapy					
DMARD monotherapy	√	√	√	√	√
Combination DMARDs§	√	√	√	√	√
Anti-TNF biologics¶	√	√	√	√	√
Non-TNF biologics#	√	√	√	√	√
While already taking therapy					
DMARD monotherapy	√	√	√	√	√
Combination DMARDs	√	√	√	√	√
Anti-TNF biologics¶	√	√	√	√	Not recommended**
Non-TNF biologics#	√	√	√	√	Not recommended**

Singh et al, Arthritis Care & Research 2012

Συστάσεις για τον εργαστηριακό έλεγχο πριν την έναρξη και κατά τη διάρκεια της αγωγής με DMARDs

Table 4. Recommendations on baseline evaluation for starting, resuming, or significant dose increase of a therapy in patients with rheumatoid arthritis receiving nonbiologic and biologic disease-modifying antirheumatic drugs*

Therapeutic agents	CBC	Liver transaminases	Creatinine	Hepatitis B and C testing†	Ophthalmologic examination‡
Hydroxychloroquine	X	X	X		X
Leflunomide	X	X	X	X	
Methotrexate	X	X	X	X	
Minocycline	X	X	X		
Sulfasalazine	X	X	X		
All biologic agents	X	X	X		

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

Table 6. Recommendations for optimal followup laboratory monitoring intervals for complete blood count, liver transaminase levels, and serum creatinine levels for rheumatoid arthritis patients receiving nonbiologic disease-modifying antirheumatic drugs*

Therapeutic agents†	Monitoring interval based on duration of therapy		
	<3 months	3–6 months	>6 months
Hydroxychloroquine	None after baseline	None	None
Leflunomide	2–4 weeks	8–12 weeks	12 weeks
Methotrexate	2–4 weeks	8–12 weeks	12 weeks
Minocycline	None after baseline	None	None
Sulfasalazine	2–4 weeks	8–12 weeks	12 weeks

Saag et al. Arthritis & Rheumatism (Arthritis Care & Research) 2008

Recommendations for contraindications to starting or resuming therapy with nonbiologic and biologic disease modifying antirheumatic drugs in RA patients

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

Organ system and contraindication	ABA	Anti-TNFα	HCQ	LEF	MTX	MIN	RIT	SSZ
Infectious diseases and pneumonitis								
Acute serious bacterial infection or infection, currently receiving antibiotics	X	X	–	X	X	–	X	–
Upper respiratory tract infection (presumed viral) with fever (>101°F)	X	X	–	–	–	–	X	–
Nonhealed infected skin ulcer	X	X	–	–	–	–	X	–
Latent TB infection prior to initiation of latent TB initiation treatment, or active TB disease prior to completing a standard regimen of anti-TB therapy†	X	X	–	X	X	–	X	–
Active life-threatening fungal infection	X	X	–	X	X	–	X	–
Active herpes-zoster viral infection	X	X	–	X	X	–	X	–
Interstitial pneumonitis (due to RA or unknown cause) or clinically significant pulmonary fibrosis	–	–	–	–	X	–	–	–
Hematologic and oncologic								
White blood cell count <3,000/mm^3‡	–	–	–	X	X	–	–	–
Platelet count <50,000/mm^3	–	–	–	X	X	–	–	X
Myelodysplasia	–	–	–	X	X	–	–	–
Treated lymphoproliferative disease of ≤5 years	–	X	–	X	X	–	–	–
Cardiac								
Moderate to severe heart failure (NYHA III or IV) and left ventricular ejection fraction <50%§	–	X	–	–	–	–	–	–

Singh et al, Arthritis Care & Research 2012

Recommendations for contraindications to starting or resuming therapy with nonbiologic and biologic disease modifying antirheumatic drugs in RA patients

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

Organ system and contraindication	ABA	Anti-TNFα	HCQ	LEF	MTX	MIN	RIT	SSZ
Liver								
Liver transaminase level 2 times the upper limit of normal	–	–	–	X	X	–	–	X
Acute hepatitis B or C viral infection	X	X	–	X	X	X	X	X
Chronic hepatitis B viral infection, receiving therapy¶								
Child-Pugh class A#	–	–	–	X	X	–	–	–
Child-Pugh class B or C	X	X	–	X	X	X**	X	X**
Chronic hepatitis B viral infection, not receiving therapy								
Child-Pugh class A	–	–	–	X	X	X	–	X
Child-Pugh class B or C	X	X	X**	X	X	X	X	X
Chronic hepatitis C viral infection, receiving therapy								
Child-Pugh class A	–	–	–	X	X	–	–	–
Child-Pugh class B or C	X	X	–	X	X	X**	X	X
Chronic hepatitis C viral infection, not receiving therapy								
Child-Pugh class A	–	–	–	X	X	X	–	–
Child-Pugh class B or C	X	X	X**	X	X	X	X	X
Renal								
Creatinine clearance <30 ml/minute	–	–	–	–	X	–	–	–
Neurologic								
Multiple sclerosis or other demyelinating disorder	–	X	–	–	–	–	–	–
Pregnancy and breastfeeding								
Planning for or current pregnancy	–	–	–	X	X	X	–	–
Breastfeeding	–	–	–	X	X	X	–	–

Singh et al, Arthritis Care & Research 2012

Revised Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy

- toxicity is cumulative with a dose greater than 1000 gr and duration of treatment over 7 years
- The AAO recommends that the following factors be taken into consideration when assessing increased risk for hydroxychloroquine toxicity: cumulative dose of 1000 g, treatment for more than 7 years, obesity, significant liver or kidney disease or advanced age, and pre- existing retinal, macular disease or cataracts.
- All individuals starting these drugs should have a complete baseline ophthalmologic examination within the first year of treatment including examination of the retina through a dilated pupil and testing of central visual field sensitivity by an automated threshold central visual field testing (Humphrey 10-2 testing).
- Examination by Amsler grid is no longer recommended
- examination by an objective test such as multifocal electroretinography (mfERG), spectral domain optical coherence tomography (SD- OCT), or fundus autofluorescence testing (FAF) is also recommended.
- If the patient is considered low risk and these examination results are normal, the AAO recommendation is that no further special ophthalmologic testing for HCQ toxicity is needed for the next 5 years.
- For patients who are considered high risk, annual eye examination is recommended without the initial 5 year delay.

Ophthalmology 2011;118:415-422.

Recommendations for monitoring hepatic toxicity in patients with rheumatoid arthritis (RA) receiving methotrexate

A. Baseline
   1. Tests for all patients
      a. Liver blood tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, albumin, bilirubin), hepatitis B and C serological studies.
      b. Other standard tests, including complete cell count and serum creatinine.
   2. Pretreatment liver biopsy (Menghini suction-type needle) only for patients with:
      a. Prior excessive alcohol consumption
      b. Persistently abnormal baseline AST values
      c. Chronic hepatitis B or C infection.

B. Monitor AST, ALT, albumin at 4–8 week intervals

C. Perform liver biopsy if:
   1. Five of nine determinations of AST within a given 12 month interval (six of 12 if tests are performed monthly) are abnormal (defined as an increase above the upper limit of normal)
   2. There is a decrease in serum albumin below the normal range (in the setting of well controlled RA)

D. If results of liver biopsy are:
   3. Roenigk grade I, II, or IIA, resume methotrexate and monitor as in B, C1, and C2 above.
   4. Roenigk grade IIIB or IV, discontinue methotrexate

E. Discontinue methotrexate in patients with persistent liver test abnormalities, as defined in C1 and C2 above, or who refuse liver biopsy

Kremer J M, Alacron G S, Lightfoot R W, et al. Arthritis Rheum 1994;

Αν επιτευχθεί η ύφεση;

Τα DMARDs διακόπτονται (;) τελευταία

12	If a patient is in persistent remission, after having tapered GCs, one can consider tapering biological DMARDs‡, especially if this treatment is combined with a synthetic DMARD
13	In cases of sustained long-term remission, cautious titration of synthetic DMARD dose could be considered, as a shared decision between patient and doctor

Smolen JS, Landewé R, Breedveld FC, *et al*. *Ann Rheum Dis* (2010)

μηνύματα

- **Στόχος της θεραπείας της ΡΑ είναι η ύφεση ή η χαμηλή ενεργότητα της νόσου**
- **Η MTX είναι το DMARD πρώτης επιλογής στις περισσότερες οδηγίες**
- **Ο θεραπευτικός στόχος επιτυγχάνεται με υψηλές δόσεις MTX > 20 mg/wk**
- **Η υψηλή δόση της MTX προτιμότερο είναι να χορηγείται υποδόρια**
- **Τα υπόλοιπα DMARDs (LEF, SSZ, HCQ, CSA, AZA) δεν αποτελούν υποδεέστερες επιλογές**
- **Οι κατευθυντήριες οδηγίες και οι συστάσεις δεν στοχεύουν στην υπόδειξη της αγωγής συγκεκριμένων ασθενών**

Πόσο δεσμευτικές είναι οι συστάσεις;

- Clinical practice guidelines are **developed to reduce inappropriate care**, minimize geographic variations in practice patterns, and enable effective use of health care resources.
- Guidelines and recommendations developed and/or endorsed by the ACR are **intended to provide guidance for particular patterns of practice** and **not to dictate the care of a particular patient.**
- The ACR considers **adherence** to these guidelines and recommendations to be **voluntary**, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances.
- Guidelines and recommendations are intended to promote beneficial or desirable outcomes but **cannot guarantee any specific outcome**.