ΑΚΑΛΥΠΤΕΣ ΘΕΡΑΠΕΥΤΙΚΕΣ ΑΝΑΓΚΕΣ ΣΤΗΝ ΡΑ

Γενική επισκόπηση της βιβλιογραφίας

ΣΠΥΡΟΣ Ν ΝΙΚΑΣ
ΡΕΥΜΑΤΟΛΟΓΟΣ
MSUS specialist
Επιστ Συνεργάτης Ρ/κ κλινικής ΠΠΓΝΙ
ΙΩΑΝΝΙΝΑ
snnikas@yahoo.com

ΣΥΓΚΡΟΥΣΗ ΣΥΜΦΕΡΟΝΤΩΝ (2y)

BMS (4/15)

Amgen (5/15)

MSD (11/15)

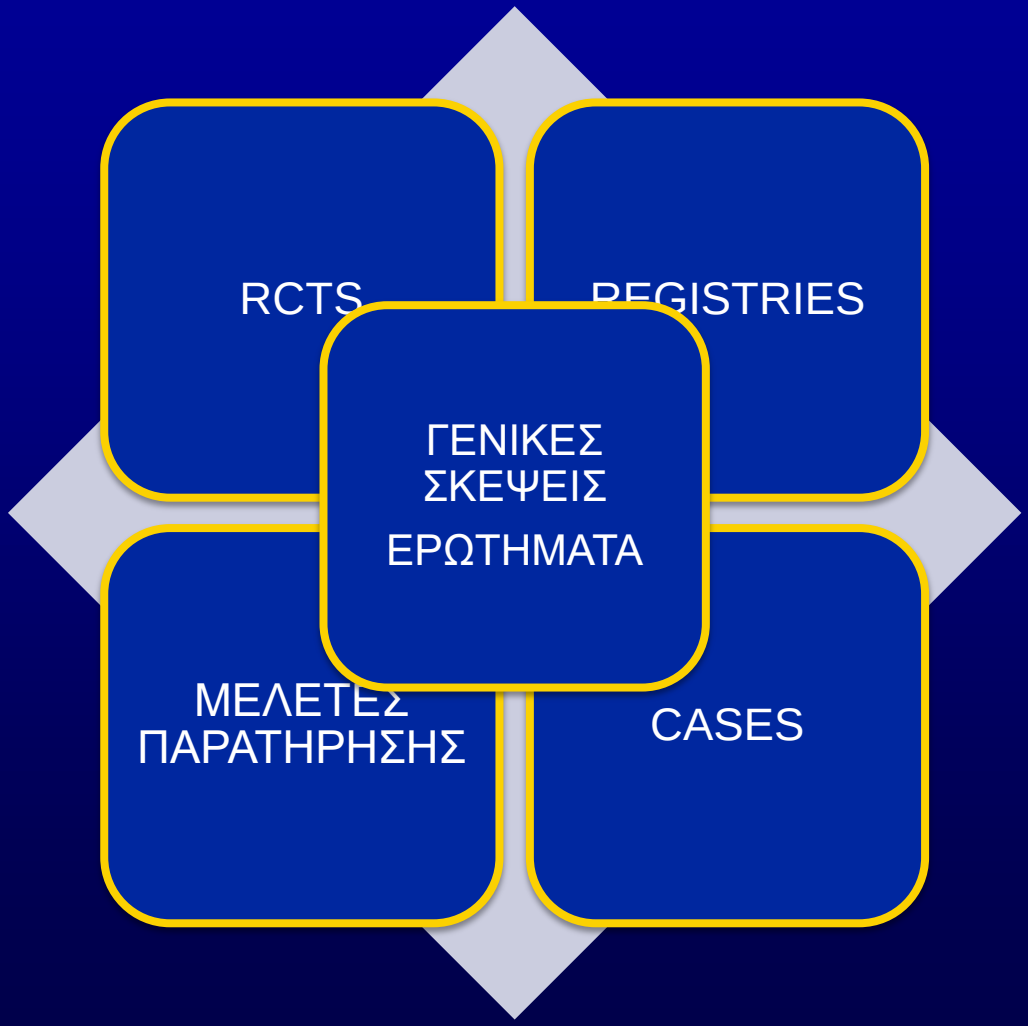
ROCHE (10/15)

BIANEΞ (10 /14)

ENORASIS (5/15)

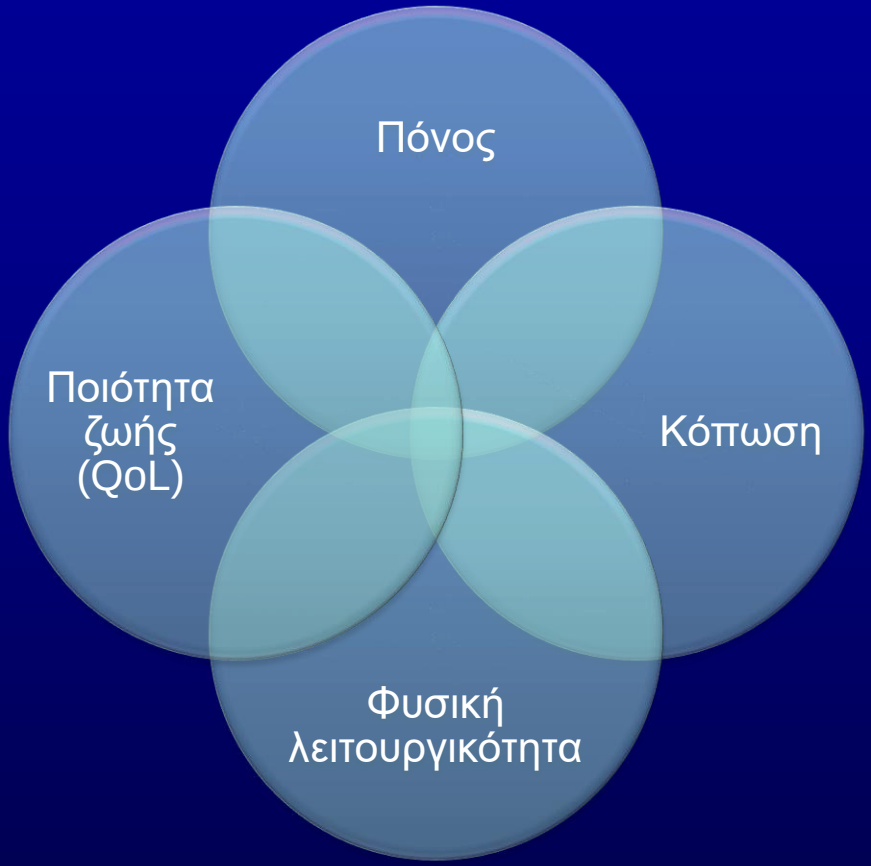
PFIZER (6/15)

ΔΕΔΟΜΕΝΑ ΣΤΗΝ ΙΑΤΡΙΚΗ



Ανεκπλήρωτες ανάγκες στην PA

RA ασθενείς/ ΣΗΜΑΝΤΙΚΑ

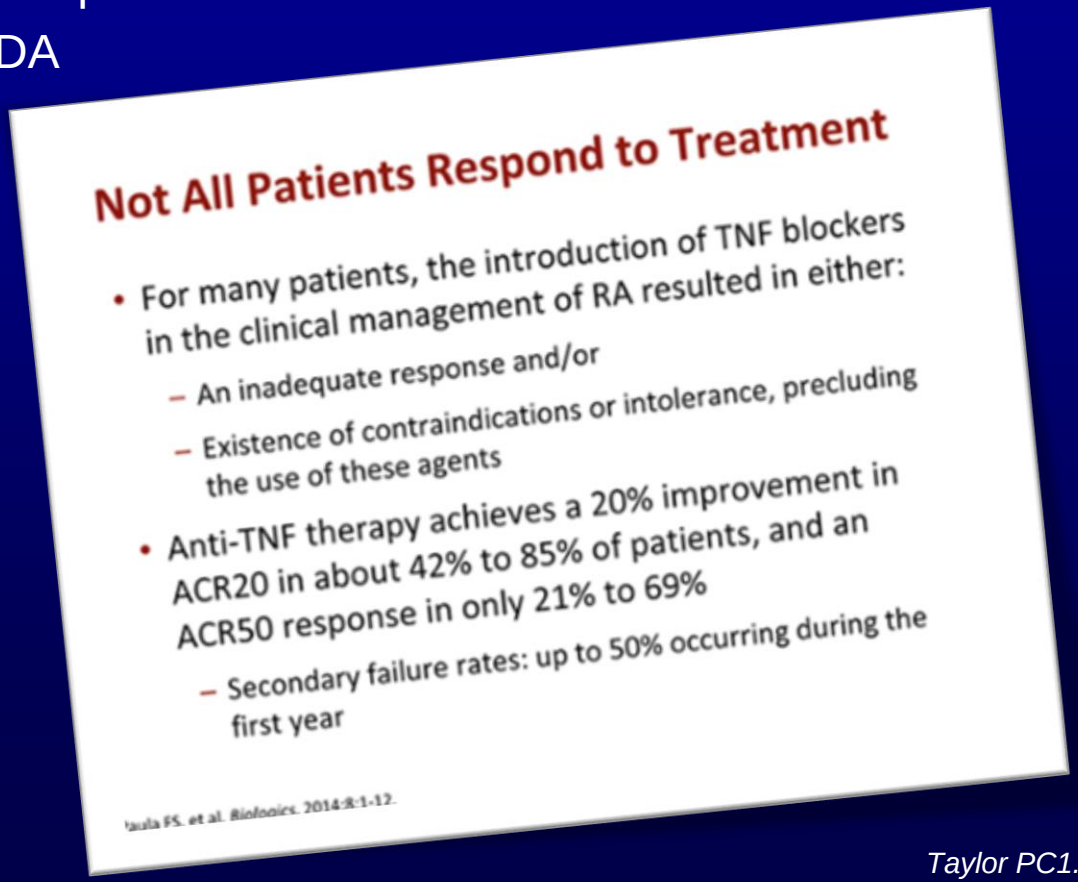


Ανεκπλήρωτες ανάγκες (ασθενείς & κλινικοί & φαρμ. εταιρείες)

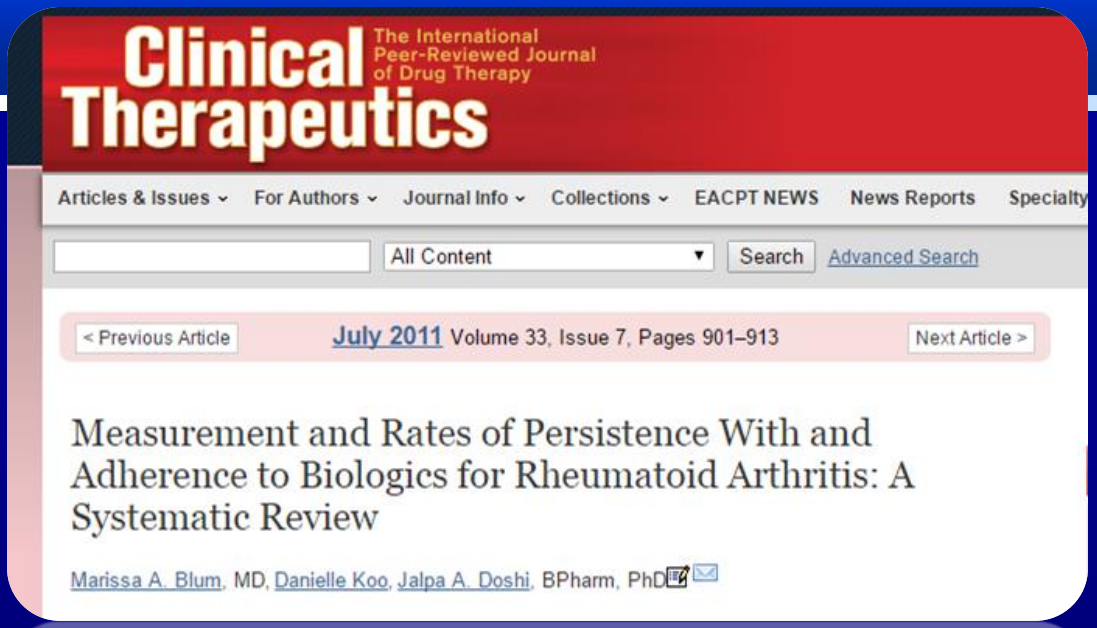
Και ενώ τα επιτεύγματα στις εκβάσεις στην RA συνεχίζουν να βελτιώνονται ,

Το επιθυμητό στόχο ΔΕΝ τον «φτάνουν» όλοι οι ασθενείς

- ύφεση
- LDA



Taylor PC1. Rheumatol Int. 2016 May;36(5):685-95



median drug survival

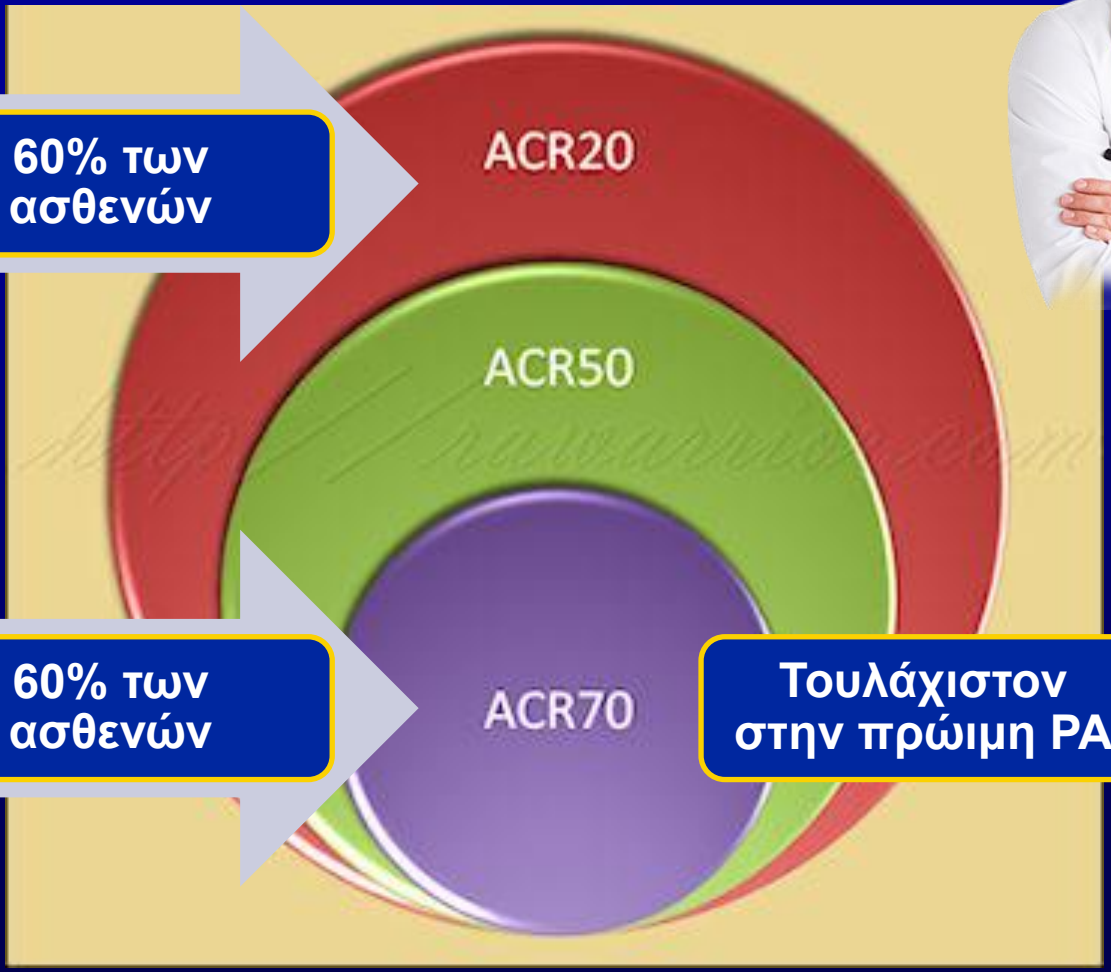
across all biologics was typically

between 32 and 39 months

ΚΑΘΕ 3 ΧΡΟΝΙΑ => ΑΛΛΑΓΗ ΒΙΟΛΟΓΙΚΟΥ !!!

Ανεκπλήρωτες ανάγκες PA (κλινικοί)

60% των ασθενών



60% των ασθενών

Τουλάχιστον στην πρώιμη PA

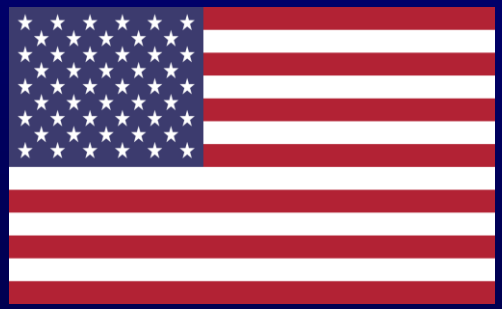
Ανεκπλήρωτες ανάγκες (κλινικοί)

ΣΤΑΤΙΣΤΙΚΑ ΣΗΜΑΝΤΙΚΟ !

1

1+ 1 2

Ανάπτυξη 100%



50

50+ 1 51

Ανάπτυξη 2 %

BMJ

BMJ 2014;348:g2130 doi: 10.1136/bmj.g2130 (Published 14 March 2014)

ENDGAMES

STATISTICAL QUESTION

Clinical significance versus statistical significance

Philip Sedgwick *reader in medical statistics and medical education*

Centre for Medical and Healthcare Education, St George's, University of London, London, UK

P value : significance versus no significance

and it **does not show how important**

the result of the statistical analysis is.

Ανεκπλήρωτες ανάγκες (κλινικοί)

ΔΕΝ Ε΄ΙΝΑΙ ΜΟΝΟ Η ΣΤΑΤΙΣΤΙΚΗ

ΤΙ ΠΡΕΠΕΙ ΝΑ ΛΑΜΒΑΝΟΥΜΕ ΥΠΟΨΗ

- **Minimal clinically important difference** (MCID) values =>
  - to assess the magnitude of changes over time

- **patient acceptable symptom state** (PASS)
  - available to determine whether the observed values would be acceptable to patients with RA

ΠΡΕΠΕΙ ΝΑ ΡΩΤΑΜΕ ΤΟΝ ΑΣΘΕΝΗ

Taylor PC1. Rheumatol Int. 2016 May;36(5):685-95

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RESEARCH ARTICLE | OPEN ACCESS

Effects of tofacitinib monotherapy on patient-reported outcomes in a randomized phase 3 study of patients with active rheumatoid arthritis and inadequate responses to DMARDs

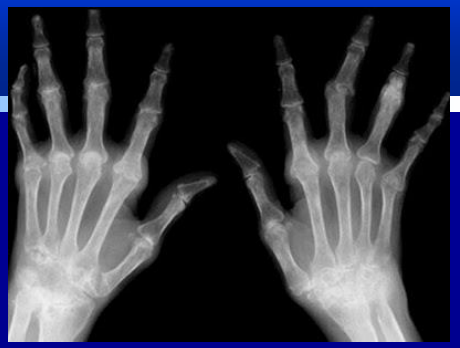
Vibeke Strand, Joel Kremer, Gene Wallenstein ✉, Keith S. Kanik, Carol Connell, David Gruben, Samuel H. Zwillich and Roy Fleischmann

Arthritis Research & Therapy 2015 **17**:307 | **DOI:** 10.1186/s13075-015-0825-9 | © Strand et al. 2015

Received: 18 December 2014 | **Accepted:** 16 October 2015 | **Published:** 4 November 2015

Tofacitinib monotherapy in DMARD-IR patients resulted in **statistically significant and clinically meaningful** improvements in multiple PROs versus placebo at month 3, with sustained improvements over 6 months

ΣΤΑΤΙΣΤΙΚΟ VS ΚΛΙΝΙΚΑ ΣΗΜΑΝΤΙΚΟ



Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial

Ronald F van Vollenhoven, Pierre Geborek, Kristina Forslind, Kristina Albertsson, Sofia Ernestam, Ingemar F Petersson, Katerina Chatzidionysiou, Johan Bratt, for the Swefot study group

Lancet 2012; 379: 1712–20

Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial

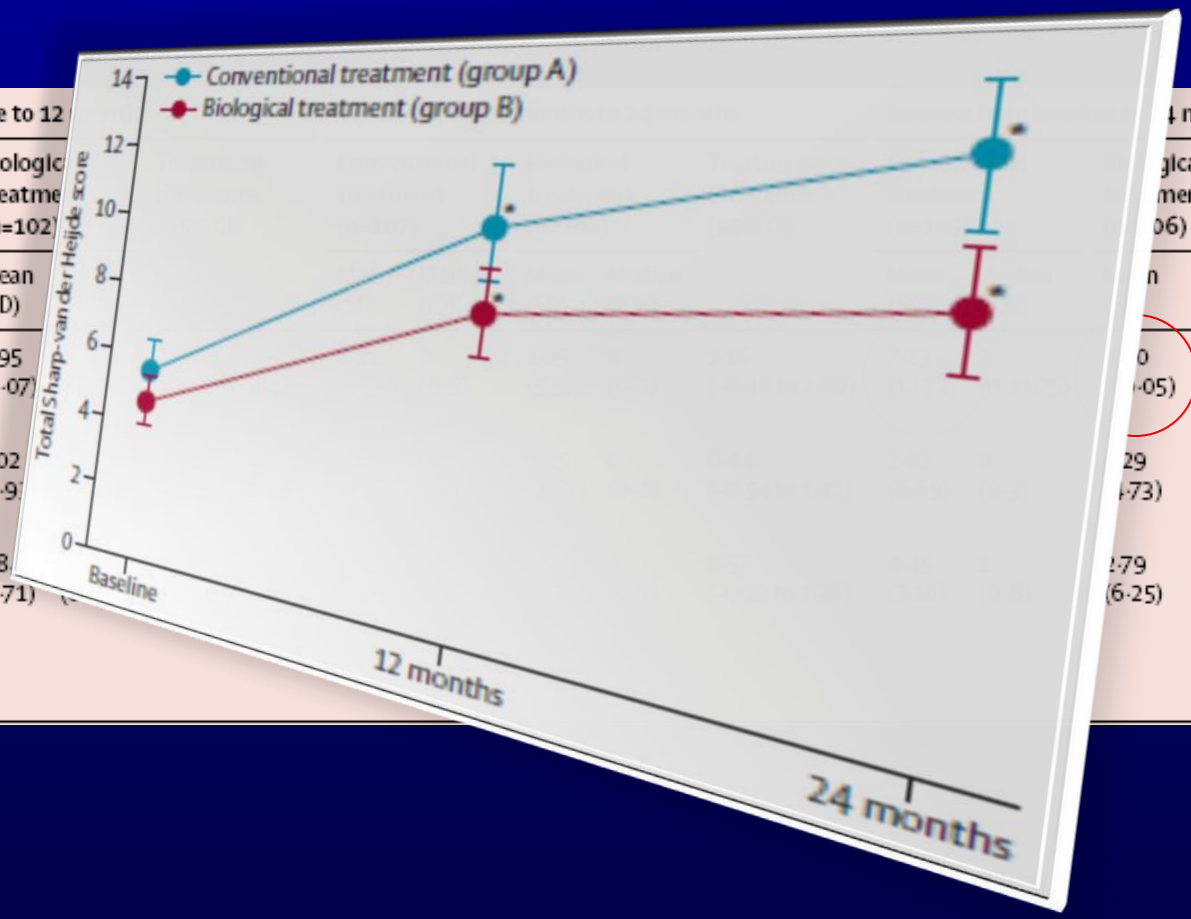
Αποτελέσματα κλινικής ανταπόκρισης

	12 months				18 months			24 months		
	Conventional treatment (n=130)	Biological treatment (n=128)	Risk ratio (95% CI)	p value	Conventional treatment (n=130)	Biological treatment (n=128)	Risk ratio (95% CI)	Conventional treatment (n=130)	Biological treatment (n=128)	p value
ACR20 response	37 (28%)	54 (42%)	1·48 (1·06–2·08)	0·0266	44 (34%)	58 (45%)	1·34 (0·99–1·82)	43 (33%)	51 (40%)	0·259
ACR50 response	19 (15%)	32 (25%)	1·71 (1·02–2·86)	0·0424	25 (19%)	39 (30%)	1·58 (1·02–2·46)	28 (22%)	38 (30%)	0·134
ACR70 response	9 (7%)	15 (12%)	1·69 (0·77–3·73)	0·2044	14 (11%)	22 (17%)	1·60 (0·86–2·98)	18 (14%)	21 (16%)	0·566
EULAR good response	32 (25%)	50 (39%)	1·59 (1·10–2·30)	0·0160	38 (29%)	49 (38%)	1·31 (0·93–1·85)	40 (31%)	49 (38%)	0·204
EULAR good to moderate response	64 (49%)	77 (60%)	1·22 (0·98–1·53)	0·0817	61 (47%)	74 (58%)	1·23 (0·97–1·56)	65 (50%)	75 (59%)	0·166

Data are n (%). ACR= American College of Rheumatology. EULAR= European League Against Rheumatism.

Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial

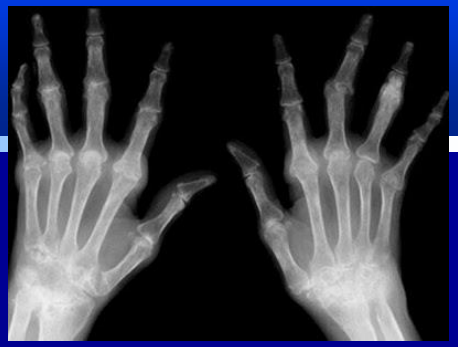
Αποτελέσματα α-α ανταπόκρισης



	Increase from baseline to 12				4 months		
	Conventional treatment (n=104)		Biologic treatme (n=102)		gical ment 06)		Treatment difference (95% CI); p value
	Mean (SE)	Median (IQR)	Mean (SD)		n	Median (IQR)	
Total score	5·04 (10·64)	1 (0–6·5)	2·95 (6·07)		0 ·05)	1 (0–5)	3·23 (0·14 to 6·32); 0·009
Erosion score	1·93 (5·28)	0 (0–2)	1·02 (2·9		29 ·73)	0 (0–1)	1·53 (–0·03 to 3·09); 0·039
Joint-space narrowing	3·12 (6·04)	0 (0–4)	1·8 (3·71)		·79 (6·25)	0 (0–4)	1·66 (–0·14 to 3·46); 0·026

p values are by Mann-Whitney *U* test.

Sharp/van der Heijde method



- The maximum erosion score is
  - 160 for the hands and wrists
  - 120 for feet
- The maximum joint space narrowing score
  - 120 for the hands and wrists
  - 48 for feet
- score ranges from 0 - 448

Increase from baseline to 24 months				
Conventional treatment (n=109)		Biological treatment (n=106)		Treatment difference (95% CI); p value
Mean (SD)	Median (IQR)	Mean (SE)	Median (IQR)	
7·23 (12·72)	3 (0–11·25)	4·00 (10·05)	1 (0–5)	3·23 (0·14 to 6·32); 0·009
2·82 (6·69)	0 (0–3)	1·29 (4·73)	0 (0–1)	1·53 (–0·03 to 3·09); 0·039
4·45 (7·10)	2 (0–8)	2·79 (6·25)	0 (0–4)	1·66 (–0·14 to 3·46); 0·026

Ann Rheum Dis. 2010 Jun;69(6):1058-64. doi: 10.1136/ard.2009.114652. Epub 2009 Aug 27.

Estimation of a numerical value for joint damage-related physical disability in rheumatoid arthritis clinical trials.

Smolen JS, Aletaha D, Grisar JC, Stamm TA, Sharp JT.

Author information

Abstract

BACKGROUND: Joint damage is an important outcome in trials of rheumatoid arthritis (RA), usually assessed by Total Sharp Score (TSS). It is currently unknown how it translates numerically into disability by the Health Assessment Questionnaire (HAQ).

OBJECTIVE: To determine the units of HAQ score corresponding to one TSS unit.

METHODS: A short-term observational trial of glucocorticoids in RA (the 'BEst LIfe with Rheumatoid Arthritis' (BELIRA) trial) was evaluated, using randomised controlled clinical trial (RCT) data for confirmation. For each trial arm HAQ, TSS and the Simplified Disease Activity Index (SDAI) were assessed. Based on the hypothesis that short-term HAQ changes will mostly be due to changes of disease activity, activity HAQ (ACT-HAQ) at end point (EP) was determined and remaining disability defined as damage related (DAM-HAQ). Using TSS at EP, the HAQ units corresponding to a TSS unit were estimated.

RESULTS: In BELIRA, one TSS unit corresponded to a mean of 0.017 HAQ units; to account for other causes of irreversible disability, the 25th percentile was used: 0.011 HAQ units/TSS unit. In RCT trial arms, the HAQ/TSS were similar (0.013 and 0.015 in established and early RA, respectively; 25th percentile: 0.010). The correlation between DAM-HAQ(EP) and TSS was r=0.829. Over 5 years, damage would amount to an increase of irreversible HAQ of 0.33 on placebo, 0.13 on disease-modifying antirheumatic drugs (DMARDs) and 0.03 on TNF inhibitors+methotrexate (MTX).

CONCLUSION: An approach to estimate the numerical relationship between HAQ and damage as 0.01 HAQ points/TSS unit is presented, although the linear relationship may not be generally valid. This allows the assessment of functional correlates of radiographic changes in trials.

EXTENDED REPORT

Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in early rheumatoid arthritis: 2-year quality-of-life results of the randomised, controlled, SWEFOT trial

Johan A Karlsson,[1] Martin Neovius,[2] Jan-Åke Nilsson,[1] Ingemar F Petersson,[1,3] Johan Bratt,[4] Ronald F van Vollenhoven,[5] Sofia Ernestam,[6] Pierre Geborek[1]

Συγκρίνοντας την προσθήκη IFX ή SSZ+HCQ

Σε ασθενείς με ενεργό PA και αποτυχία στην MTX

ΔΕΝ υπάρχει στατιστικά σημαντική διαφορά

Σε utility ή QALY

JAMA Internal Medicine
Formerly Archives of Internal Medicine

Original Investigation | August 12/26, 2013

Biological vs Conventional Combination Treatment and Work Loss in Early Rheumatoid Arthritis

A Randomized Trial

Jonas K. Eriksson, MSc[1]; Martin Neovius, PhD[1]; Johan Bratt, MD, PhD[2]; Ingemar F. Petersson, MD, PhD[3,4]; Ronald F. van Vollenhoven, MD, PhD[5]; Pierre Geborek, MD, PhD[4]; Sofia Ernestam, MD, PhD[6]

[+] Author Affiliations

JAMA Intern Med. 2013;173(15):1407-1414. doi:10.1001/jamainternmed.2013.7801.

ABSTRACT

Original Investigation | August 12/26, 2013

Biological vs Conventional Combination Treatment and Work Loss in Early Rheumatoid Arthritis

A Randomized Trial

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[+] Author Affiliations

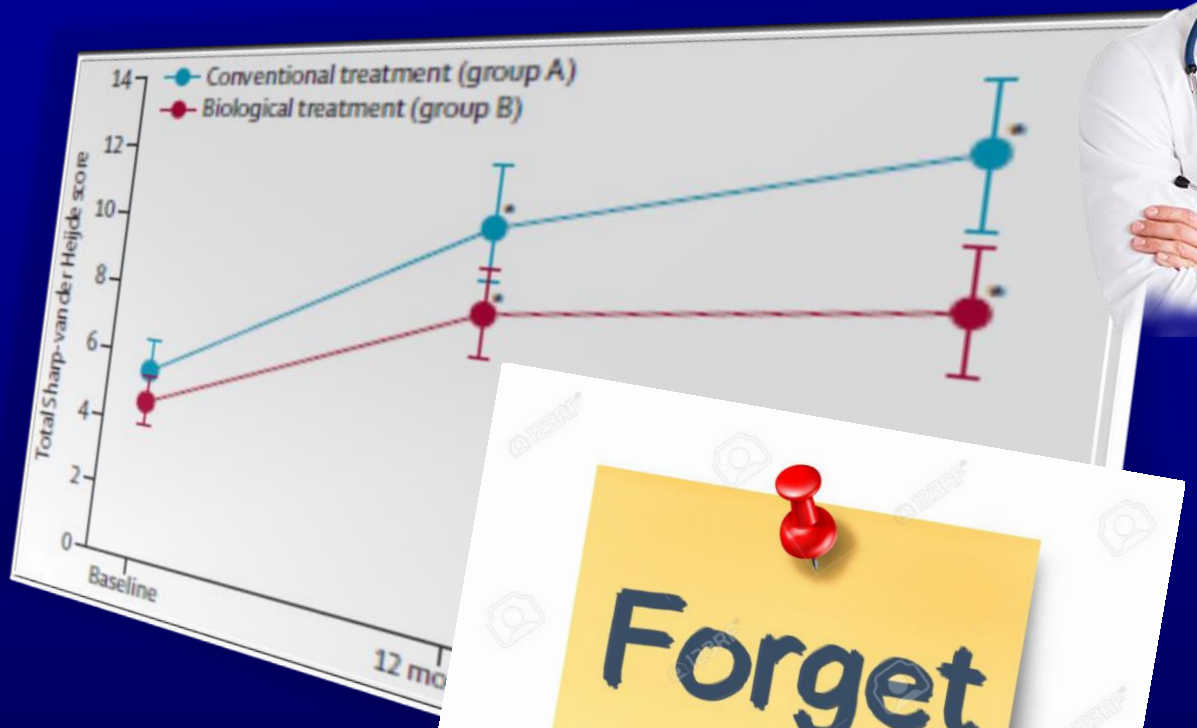
JAMA Intern Med. 2013;173(15):1407-1414. doi:10.1001/jamainternmed.2013.7801. Text Size: A A

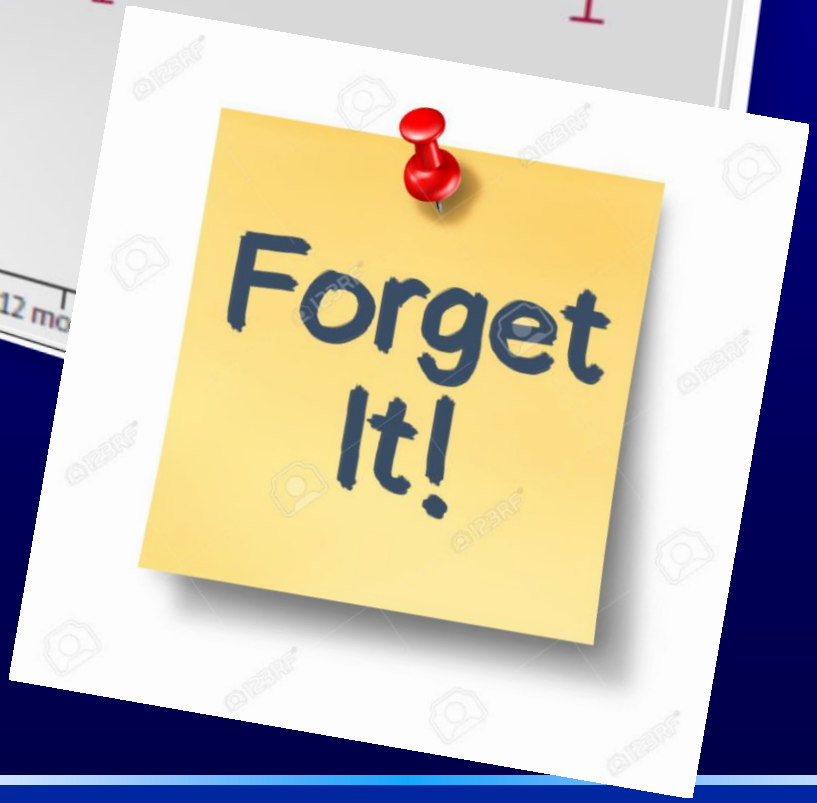
Αν και υπήρχε ακτινολογική ανωτερότητα στην ομάδα υπό βιολογικό

αυτό ΔΕΝ μεταφράζεται σε

καλύτερη εργασιακή ικανότητα

Ανεκπλήρωτες ανάγκες ΡΑ (κλινικοί)





Ανεκπλήρωτες ανάγκες PA (ΑΣΘΕΝΕΙΣ / ΠΟΝΟ)

Rheumatol Int (2016) 36:685–695
DOI 10.1007/s00296-015-3415-x

Rheumatology INTERNATIONAL

CrossMark

REVIEW ARTICLE - REVIEW ON DISEASE

A structured literature review of the burden of illness and unmet needs in patients with rheumatoid arthritis: a current perspective

Peter C. Taylor[1] · Adam Moore[2,6] · Radu Vasilescu[3] · Jose Alvir[4] · Miriam Tarallo[5]

Και ενώ βιολογικοί & MTX απαλύνουν τον πόνο=>

πολλοί ασθενείς RA **συνεχίζουν** να εκφράζουν ΜΗ ΑΝΕΚΤΟ ΕΠΙΠΕΔΟ ΠΟΝΟΥ

Overall, the current literature suggests that **pain persists** at an **unacceptable** level in patients with RA

Taylor PC. Rheumatol Int. 2016 May;36(5):685-95

ΠΟΝΟΣ ΣΤΗΝ ΡΑ

although treatment with a **biologic** in patients produced **clinically** meaningful improvements in pain

•scores remained below the **PASS*** threshold

patients with RA continue to experience moderate pain, despite ongoing treatment with **DMARDs**

*Fleischmann R (2009) The clinical effiacy and safety of **certolizumab** pegol (CZP) in the treatment of rheumatoid arthritis: focus on long-term use, patient considerations and the impact on quality of life. Open Access Rheumatol Res Rev 1:95–106*

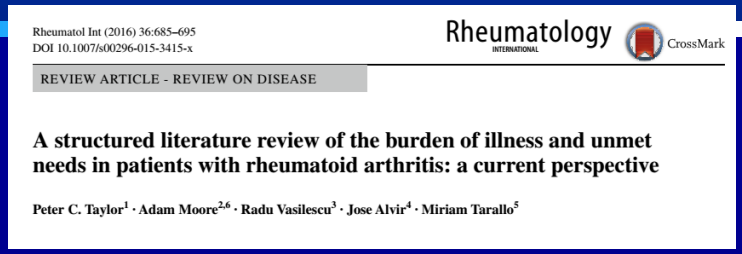
** patient acceptable symptom state : ΕΠΙΠΕΔΟ ΑΝΤΙΛΗΨΗΣ*

Στατιστικά σημαντικό

Κλινικά σημαντικό

PASS

ΦΥΣΙΚΗ ΔΡΑΣΤΗΡΙΟΤΗΤΑ



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Επιμένει σε **ΜΗ ΙΚΑΝΟΠΟΙΗΤΙΚΑ ΕΠΙΠΕΔΑ** , ειδικά σε :

those who do not achieve MCID or PASS thresholds despite ongoing treatment

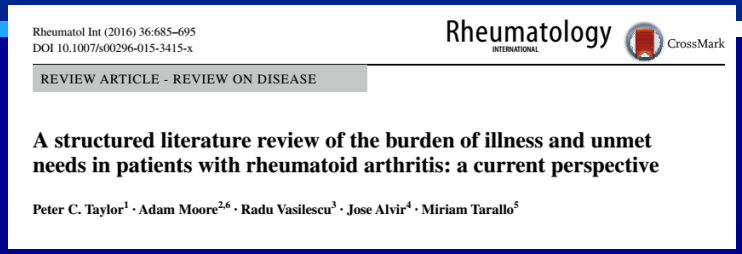
ΗΠΙΑ – ΜΕΤΡΙΑ disability :

(mean health assessment questionnaire [HAQ] score of 1.2–1.8 at baseline)

Είναι πάνω από το αποδεκτό όριο

Taylor PC1. Rheumatol Int. 2016 May;36(5):685-95

ΦΥΣΙΚΗ ΔΡΑΣΤΗΡΙΟΤΗΤΑ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Όπως και στις κλινικές μελέτες :

observational / με τη χρήση :

- patient-reported outcomes (PROs) such as the HAQ
- the medical outcomes short form-36 (SF-36)

ΑΠΟΤΥΧΙΑ ΝΑ ΕΠΙΤΕΥΧΘΟΥΝ ΤΑ ΟΡΙΑ ΤΟΥ PASS

csDMARDs & biologics

Taylor PC1. Rheumatol Int. 2016 May;36(5):685-95

ΦΥΣΙΚΗ ΔΡΑΣΤΗΡΙΟΤΗΤΑ / HAQ

Σύγχρονες θεραπείες ΑΠΟΤΥΓΧΑΝΟΥΝ συχνά να βελτιώσουν το HAQ => **clinically important margins**

with patients frequently experiencing an unacceptable level of physical disability despite ongoing treatment

Stockl KM, Shin JS, Lew HC, Zakharyan A, Harada AS, Solow BK, Curtis BS (2010) Outcomes of a rheumatoid arthritis disease therapy management program focusing on medication adherence. J Manag Care Pharm 16:593–604

Farahani P, Levine M, Gaebel K, Wang EC, Khalidi N (2006) Community-based evaluation of etanercept in patients with rheumatoid arthritis. J Rheumatol 33:665–670

ΦΥΣΙΚΗ ΔΡΑΣΤΗΡΙΟΤΗΤΑ/ HAQ

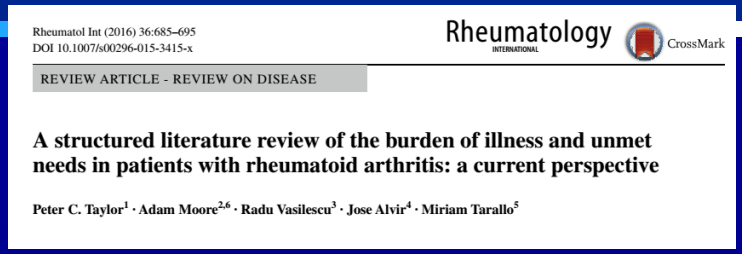
47 % των ασθενών απέτυχαν να φτάσουν : **HAQ levels ενδεικτικό**:

- minimal residual disease activity
- *a secondary goal of treatment for patients unlikely to achieve remission*

Bae SC, Gun SC, Mok CC, Khandker R, Nab HW, Koenig AS, Vlahos B, Pedersen R, Singh A (2013) Improved health outcomes with etanercept versus usual DMARD therapy in an Asian population with established rheumatoid arthritis. BMC Musculoskelet Disord 14:13.

Pavelka K, et al. (2013) Induction of response with etanercept-methotrexate therapy in patients with moderately active rheumatoid arthritis in Central and Eastern Europe in the PRESERVE study. Clin Rheumatol 32:1275–1281.

ΝΟΗΤΙΚΗ ΔΡΑΣΤΗΡΙΟΤΗΤΑ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16 άρθρα

suboptimal mental health persists in a substantial proportion of patients with RA /

mental health subdomain of the SF-36

- 48–92 % of patients who **remained on MTX —**despite meeting eligibility criteria for treatment with biologics—did not meet MCID thresholds

- 35–66 % of patients **failed** to meet **MCID** thresholds across 6 clinical trials of **biologic** treatments

Strand V, Singh JA (2010) Newer biological agents in rheumatoid arthritis: impact on health-related quality of life and productivity. Drugs 70:121–145.

ΚΟΠΩΣΗ

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ΚΛΙΝΙΚΕΣ ΜΕΛΕΤΕΣ

biologics, in combination with MTX,

ΑΠΟΤΥΧΊΑ: **meaningful improvements** in fatigue

Η ΚΟΠΩΣΗ ΣΥΝΕΧΙΖΕΙ ΝΑ ΕΧΕΙ :

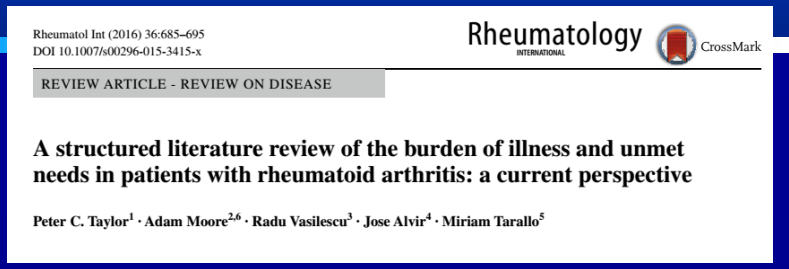
- considerable **negative impact** on > 50% of patients with RA
- and is a major determinant of QoL

fatigue-related endpoints were

rarely reported in clinical trials

Carr A, Hewlett S, Hughes R, Mitchell H, Ryan S, Carr M, Kirwan J (2003) Rheumatology outcomes: the patient's perspective. J Rheumatol 30:880–883

ΚΟΙΝΩΝΙΚΗ ΔΡΑΣΤΗΡΙΟΤΗΤΑ


Rheumatol Int (2016) 36:685–695
DOI 10.1007/s00296-015-3415-x

Rheumatology INTERNATIONAL

REVIEW ARTICLE - REVIEW ON DISEASE

A structured literature review of the burden of illness and unmet needs in patients with rheumatoid arthritis: a current perspective

Peter C. Taylor[1] · Adam Moore[2,6] · Radu Vasilescu[3] · Jose Alvir[4] · Miriam Tarallo[5]

1 μελέτη => ΝΟΣΟΣ : **negative impact** on relationships with friends and family was reported by approximately on **1/5** of patients with RA

McInnes IB, et al (2013) Understanding the patient perspective—results of the Rheumatoid Arthritis: Insights, Strategies & Expectations (RAISE) patient needs survey. Clin Exp Rheumatol 31:350–357

PASS values for social functioning **were met in 1 /10** studies and were achieved only in a subpopulation of the overall sample who had been receiving MTX at the start of the study period

da Mota LM, et al (2012). Rheumatol Int 32:3937–3943

ΣΕΞΟΥΑΛΙΚΗ ΔΡΑΣΤΗΡΙΟΤΗΤΑ

observational study of sexual activity and sexual dysfunction in patients with RA receiving treatment with **biologics or DMARDs**

- 53.8 % of men and 45.7 % of women experienced some form of sexual **dysfunction**
  - in response to a multidimensional patient-reported outcome measures questionnaire

El Miedany Y, El Gaafary M, El Aroussy N, Youssef S, Ahmed I (2012) Sexual dysfunction in rheumatoid arthritis patients: arthritis and beyond. Clin Rheumatol 31:601–60

ΣΕΞΟΥΑΛΙΚΗ ΔΡΑΣΤΗΡΙΟΤΗΤΑ

One survey :

- 22 % of biologic-experienced
- 16 % of biologic-naïve patients (P ≤ 0.05)

experienced **problems with sexual function**

McInnes IB, Combe B, Burmester G (2013) Understanding the patient perspective—results of the Rheumatoid Arthritis: Insights, Strategies & Expectations (RAISE) patient needs survey. Clin Exp Rheumatol 31:350–357

Ο ΡΟΛΟΣ ΤΩΝ ΑΣΘΕΝΩΝ ΣΤΗΝ ΘΕΡ. ΑΠΟΦΑΣΗ

Table 1 2013 Update of the EULAR recommendations (the table of 2010 recommendations ca… original publication)

Overarching principles

A. Treatment of RA patients should aim at the best care and must be based on a shared decision between the patient and the rheumatologist

B. Rheumatologists are the specialists who should primarily care for RA patients

C. RA incurs high individual, societal and medical costs, all of which should be considered in its management by the treating rheumatologist

- support for the patient to develop **personal preferences**

- **inform** the patient of the **risks** of RA and the benefits of reaching the targeted disease activity states

based on the reviewed literature**, it was not possible** to accurately ascertain how patients gauged control of RA

RA & ΕΡΓΑΣΙΑ

ΕΊΝΑΙ ΓΝΩΣΤΟ:

- an estimated 1/3 of patients with RA terminate employment prematurely
- 5 years after diagnosis, 30–40 % of patients experience work disability

increased severity of **pain** & physical **disability =>**

were associated with greater work disability

There was evidence that **intensive treatment** strategies with a combination of DMARDs may play a crucial role in **reducing the adverse work-related** impacts of RA

Taylor PC1. Rheumatol Int. 2016 May;36(5):685-95

ΟΙΚΟΝΟΜΙΚΟ ΦΟΡΤΙΟ ΤΗΣ ΡΑ

RA is associated with a large economic burden to individual patients, their families, and to society, with an estimated total annual economic burden of

€45.3 billion in Europe

€41.6 billion in the USA

Direct costs

associated with RA include medications, hospitalizations, clinic visits, laboratory monitoring imaging, toxicity, and medical assist devices

Indirect costs

such as loss of earnings, caregiver productivity, and intangible costs arising from pain, depression and anxiety, and suboptimal QoL also contribute to the economic burden of RA

ΕΡΓΑΣΙΑ & ΟΙΚΟΝΟΜΙΚΟ ΦΟΡΤΙΟ ΣΤΗΝ ΡΑ

Rheumatol Int (2016) 36:685–695
DOI 10.1007/s00296-015-3415-x

Rheumatology INTERNATIONAL

CrossMark

REVIEW ARTICLE - REVIEW ON DISEASE

A structured literature review of the burden of illness and unmet needs in patients with rheumatoid arthritis: a current perspective

Peter C. Taylor[1] · Adam Moore[2,6] · Radu Vasilescu[3] · Jose Alvir[4] · Miriam Tarallo[5]

Οι περισσότερες μελέτες εστιάζουν

- **absenteeism** associated with the disease
- Πολύ μικρή έρευνα για το **presenteeism** or productivity

Συνοσηρότητες στην ΡΑ

οστεοπόρωση στην PA

Autoimmunity Reviews 12 (2013) 958–966

Contents lists available at SciVerse ScienceDirect

Autoimmunity Reviews

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

Review

Biologic therapies and systemic bone loss in rheumatoid arthritis

Theodoros Dimitroulas [a,*], Spyros N. Nikas [a], Panagiotis Trontzas [b], George D. Kitas [a,c]

[a] Department of Rheumatology, Dudley Group of Hospitals NHS Trust, Russells Hall Hospital, Dudley, West Midlands, UK
[b] Department of Rheumatology, Polycliniki Hospital, Athens, Greece
[c] Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, UK

Οι βιολογικοί αυξάνουν την οστική πυκνότητα vs csDMARDs

ORIGINAL ARTICLE

JBMR

Effects of Disease-Modifying Antirheumatic Drugs on Nonvertebral Fracture Risk in Rheumatoid Arthritis: A Population-Based Cohort Study

Seo Young Kim,[1,2] Sebastian Schneeweiss,[1] Jun Liu,[1] and Daniel H Solomon[1,2]

Journal of Bone and Mineral Research, Vol. 27, No. 4, April 2012, pp 789–796

PA, anti-TNF-α & κάταγμα

Among subjects diagnosed with RA

the adjusted risk of **non-vertebral fracture** was

similar

across persons starting

a TNFi , MTX or other nbDMARD

Effects of disease-modifying antirheumatic drugs on nonvertebral fracture risk in rheumatoid arthritis: a population-based cohort study. Kim SY1, Schneeweiss S, Liu J, Solomon DH J Bone Miner Res. 2012 Apr ;27(4):789-96.

PA & CVD

Curr Opin Rheumatol. 2013 May ; 25(3): 317–324. doi:10.1097/BOR.0b013e32835fd7f8.

Rheumatoid Arthritis and Cardiovascular Disease: Update on Treatment Issues

Medha Barbhaiya, MD and **Daniel H. Solomon, MD, MPH**
Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA

Abstract

Purpose of review—This review examines thresholds for treatment of traditional cardiovascular disease (CVD) risk factors among RA patients and whether RA-specific treatment modulates cardiovascular risk.

Recent findings—There are substantial data demonstrating an increased CVD risk among patients with RA. Both traditional CVD risk factors and inflammation contribute to this risk. Recent epidemiologic studies strengthen the case that aggressive immunosuppression with biologic DMARDs, such as TNF antagonists, is associated with a reduced risk of CVD events. However, to data, there are no randomized controlled trials published regarding the management of CVD in RA.

Summary—Epidemiologic evidence continues to accumulate regarding the relationship between the effects of traditional CVD risk factors and RA-specific treatments on CV outcomes in RA. The field needs randomized controlled trials to better guide management.

RA & CVD : εξατομίκευση αγωγής !

Σε συγκριτική μελέτη Tocilizumab Vs Etanercept με

- 3080 οροθετικούς PA ασθενείς (με τουλάχιστον ένα παράγοντα κινδύνου για CVD) με σκοπό την εκτίμηση του CVD κινδύνου διαπιστώθηκαν
- 83 σοβαρά καρδιαγγειακά επεισόδια (MACE) / 4900 PYs στην ομάδα υπό TCZ vs
- 78/ 4891 PYs στην ομάδα υπό ETA ((HR 1.05; 95% CI 0.77, 1.43)
- κάτι που σημαίνει αύξηση 5% **του κινδύνου στην ομάδα υπό TOC**

PA και ΣΚΑ

- Two clinical trials of etanercept in CHF patients were **stopped early**, with a pooled analysis showing a small, nonsignificant trend toward increased hospitalization and mortality at higher doses

- infliximab was ineffective in CHF patients, with the higher dose (10 mg/kg) associated with a significant increase **in risk of mortality** or CHF hospitalization

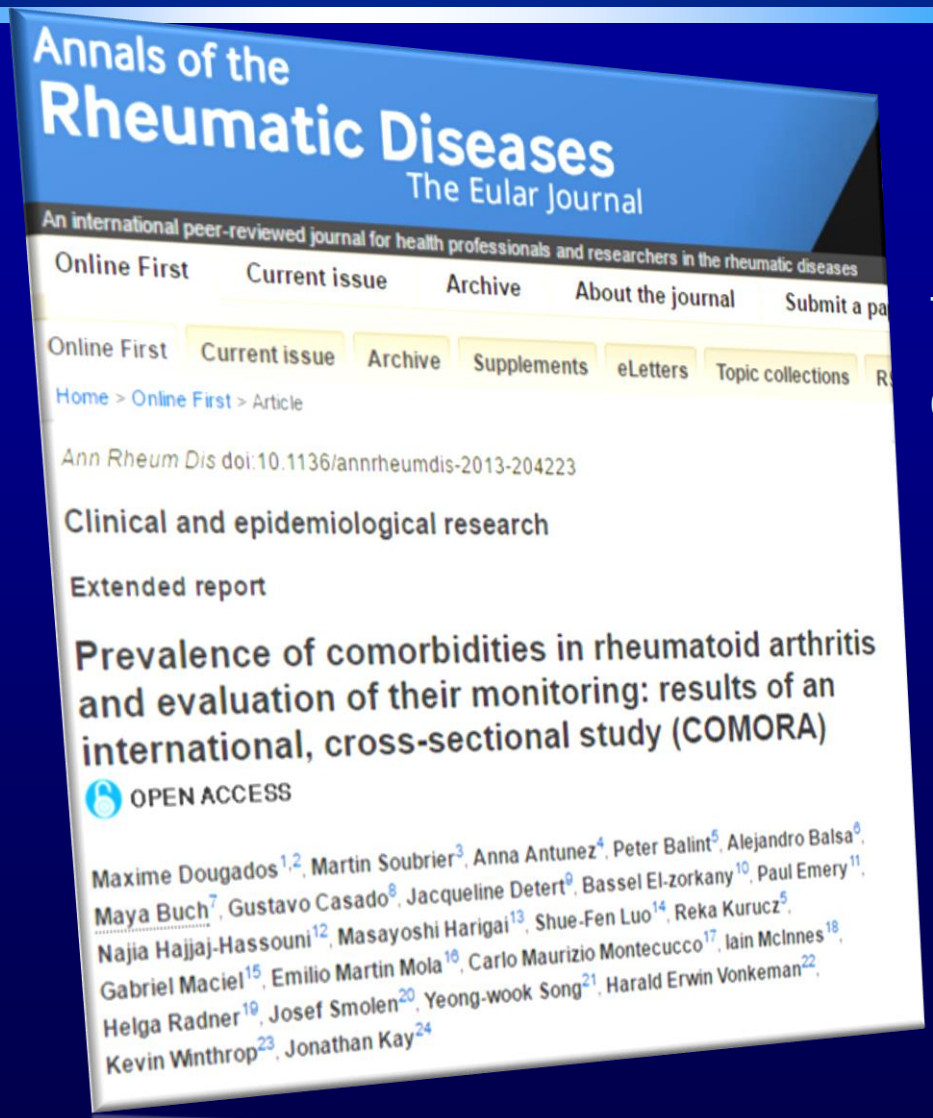
observational studies

have not convincingly shown that TNFi agents increase CHF risk in RA

particularly in the absence of pre-existing cardiovascular disease

*Unmet Needs in the Treatment of RheumatVol.3 No.2(2013), Article ID:31379,14 pages oid Arthritis*Janet Pope1,2, Bernard Combe3Open Journal of Rheumatology and Autoimmune Diseases*

PA και ΣΥΝΟΣΗΡΟΤΗΤΕΣ



The most frequently associated diseases (past or current) were:

- **depression, 15%**
- asthma, 6.6%
- cardiovascular events (myocardial infarction, stroke), 6%
- solid malignancies (excluding basal cell carcinoma), 4.5%;
- chronic obstructive pulmonary disease, 3.5%

OXFORD JOURNALS Rheumatology (Oxford, England)

Rheumatology (Oxford). 2013 Dec; 52(12): 2136–2148.
Published online 2013 Sep 3. doi: 10.1093/rheumatology/ket169

The prevalence of depression in rheumatoid arthritis: a review and meta-analysis

Faith Matcham,[✉1] Lauren Rayner,[1] Sophia Steer,[2] and Matthew Hotopf[1]

Author information ▶ Article notes ▶ Copyright and License information ▶

Abstract

Go to:

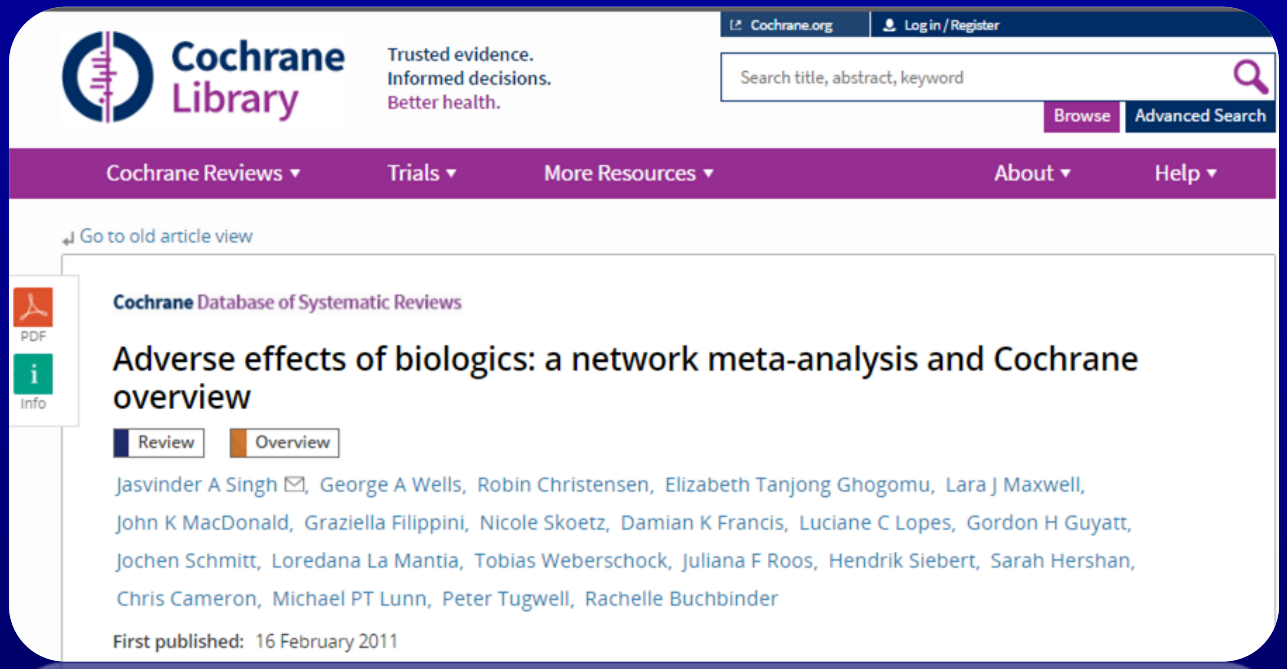
Objective. There is substantial uncertainty regarding the prevalence of depression in RA. We conducted a systematic review aiming to describe the prevalence of depression in RA.

Methods. Web of Science, PsycINFO, CINAHL, Embase, Medline and PubMed were searched for cross-sectional studies reporting a prevalence estimate for depression in adult RA patients. Studies were reviewed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines and a meta-analysis was performed.

Results. A total of 72 studies, including 13 189 patients, were eligible for inclusion in the review. Forty-three methods of defining depression were reported. Meta-analyses revealed the prevalence of major depressive disorder to be 16.8% (95% CI 10%, 24%). According to the PHQ-9, the prevalence of depression was 38.8% (95% CI 34%, 43%), and prevalence levels according to the HADS with thresholds of 8 and 11 were 34.2% (95% CI 25%, 44%) and 14.8% (95% CI 12%, 18%), respectively. The main influence on depression prevalence was the mean age of the sample.

ΑΣΧΟΛΟΥΜΑΣΤΕ ???

PA & λοιμώξεις - βιολογικοί



160 randomized clinical trials and 46 extension studies:

- biologics as a group in the standard-dose model
- were **significantly associated with increased risk of serious infection** compared with control treatment
- odds ratio 1.37

PA & TB

- TNFi therapy is associated with **increased risk** of tuberculosis due to reactivation of latent disease
- **anti-TNF monoclonal antibodies** carrying a higher risk than etanercept
- tuberculosis risk with **newer agents** appears low
- Recommendations are in place for country-specific tuberculosis screening for TNFi agents, tocilizumab, and abatacept
- screening is not necessary for rituximab

*Unmet Needs in the Treatment of RheumatVol.3 No.2(2013), Article ID:31379,14 pages oid Arthritis*Janet Pope1,2, Bernard Combe3Open Journal of Rheumatology and Autoimmune Diseases*

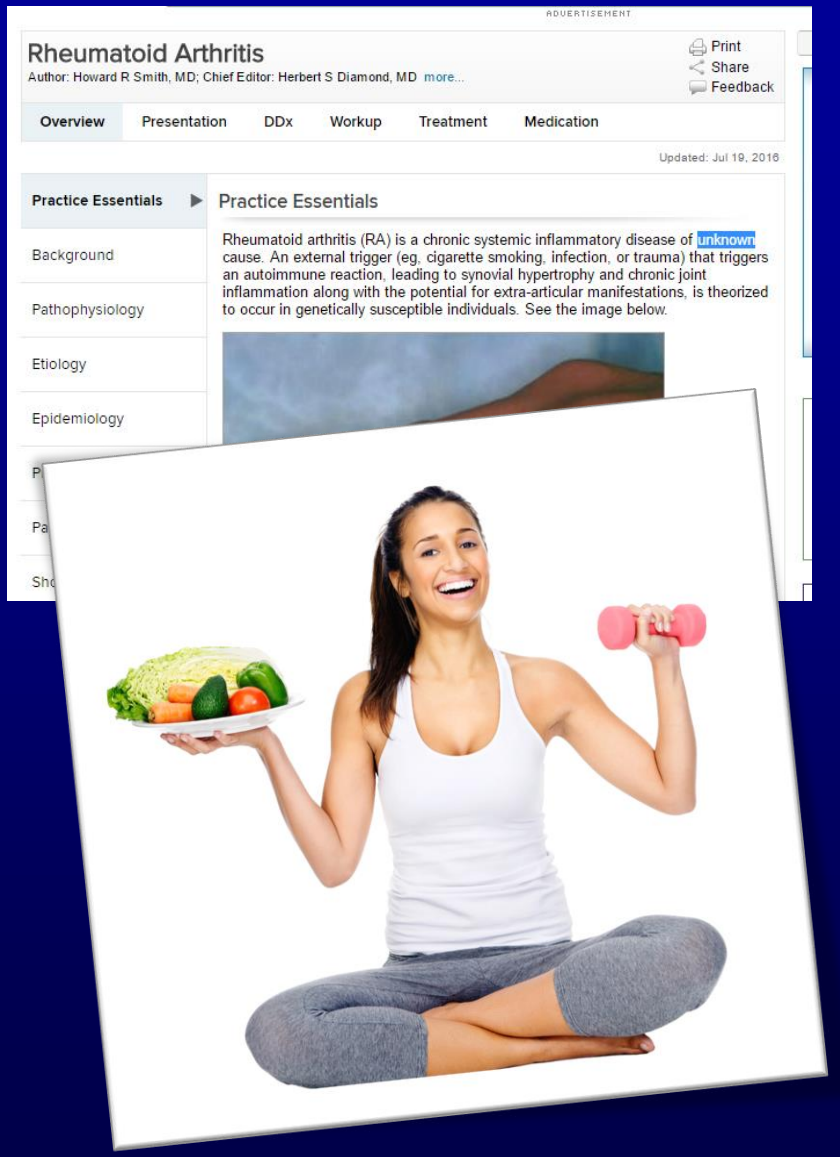
ΑΝΕΚΛΠΗΡΩΤΕΣ ΑΝΑΓΚΕΣ

ΔΙΑΦΟΡΑ / Κλινικούς

Αιτιολογία της ΡΑ

Ο ρόλος **της Διατροφής / Άσκησης**

στην ανάπτυξη ή εξέλιξη της νόσου



ΔΙΑΦΟΡΑ / Κλινικούς

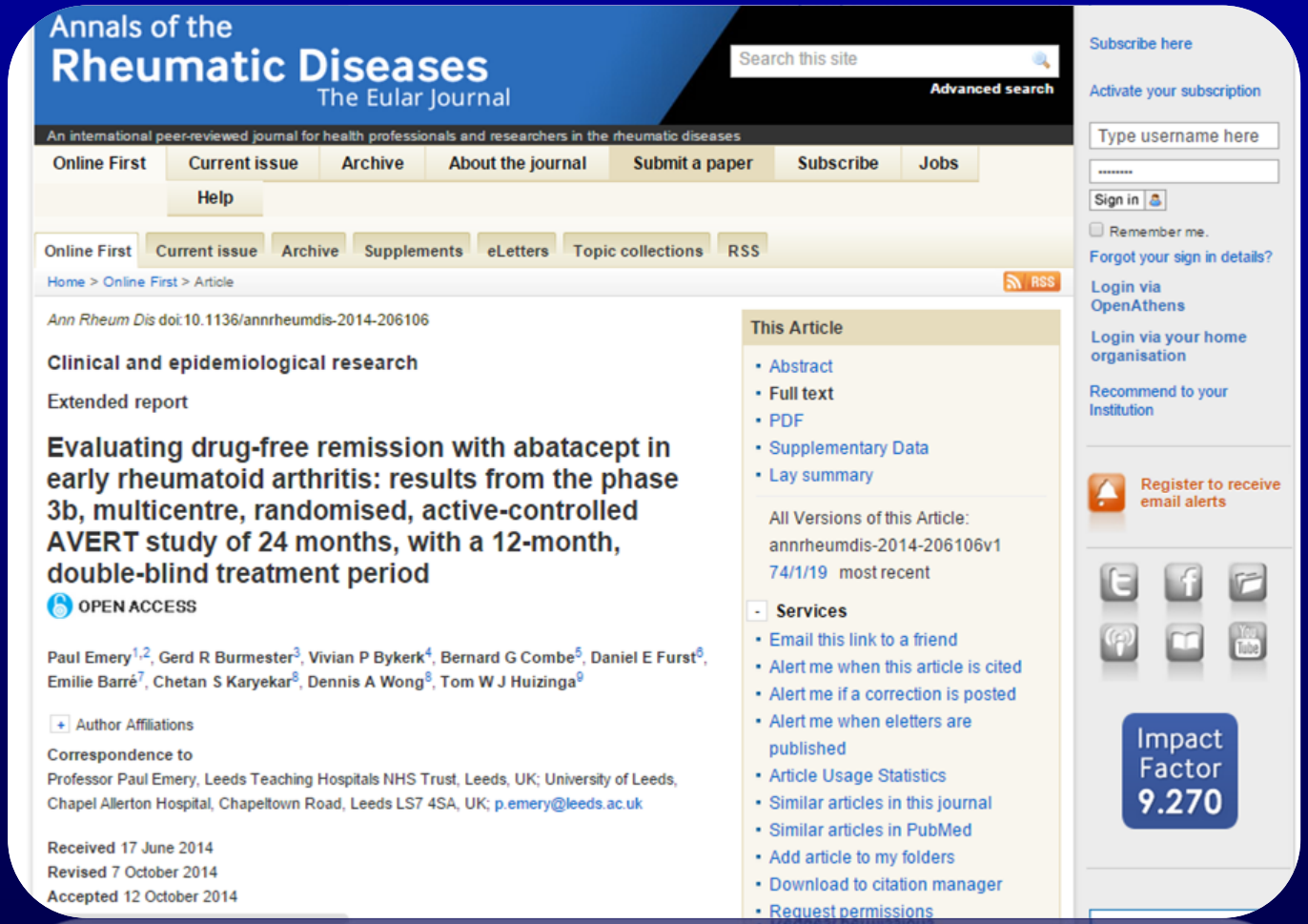
Πρόληψη

(σε ασθενείς με RF/ACPA με/χωρίς αρθραλγίες)

Θεραπεία

και όχι καταστολή νόσου

Θεραπεία και όχι …καταστολή νόσου



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Ann Rheum Dis doi:10.1136/annrheumdis-2014-206106

Clinical and epidemiological research

Extended report

Evaluating drug-free remission with abatacept in early rheumatoid arthritis: results from the phase 3b, multicentre, randomised, active-controlled AVERT study of 24 months, with a 12-month, double-blind treatment period

OPEN ACCESS

Paul Emery[1,2], Gerd R Burmester[3], Vivian P Bykerk[4], Bernard G Combe[5], Daniel E Furst[6], Emilie Barré[7], Chetan S Karyekar[8], Dennis A Wong[8], Tom W J Huizinga[9]

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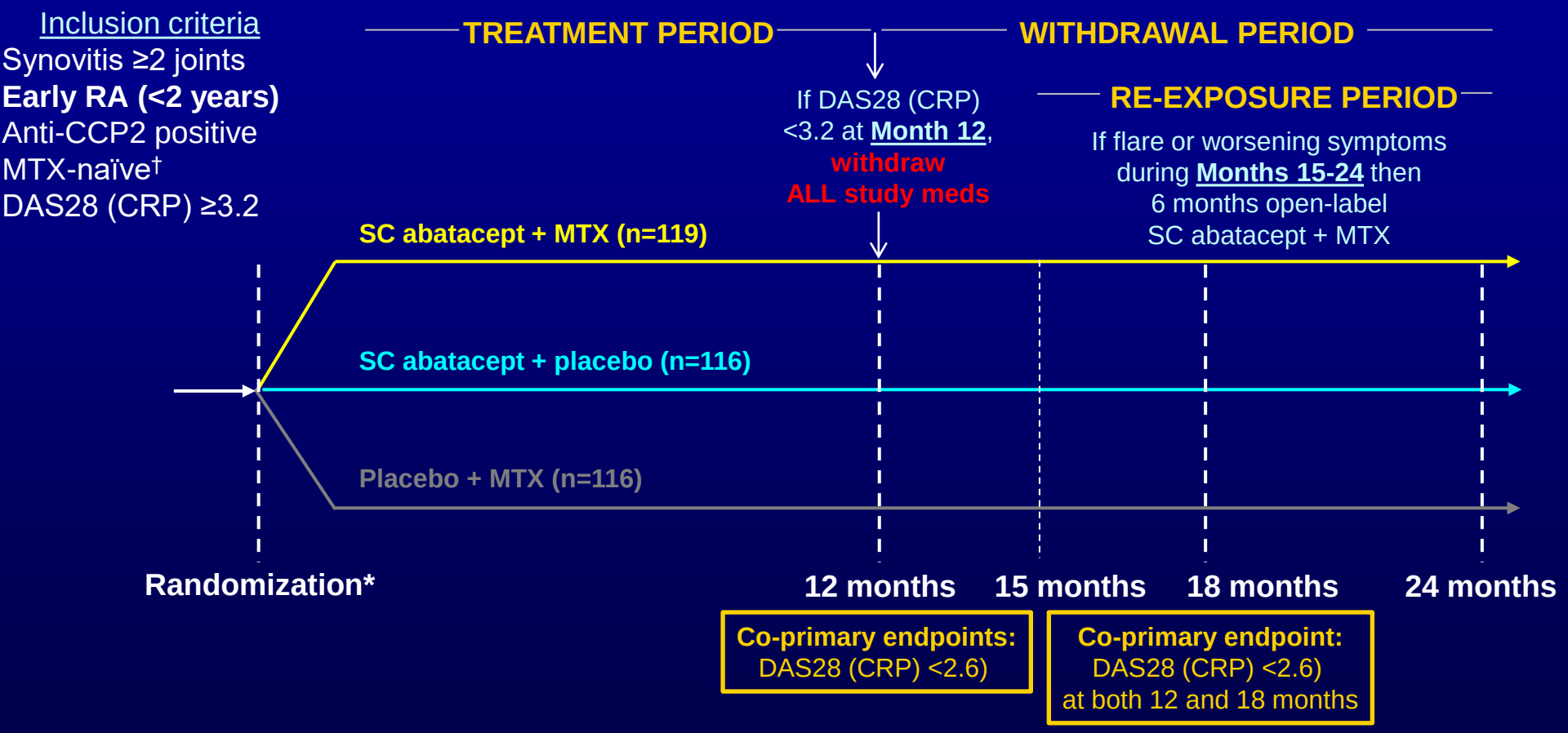
AVERT Study

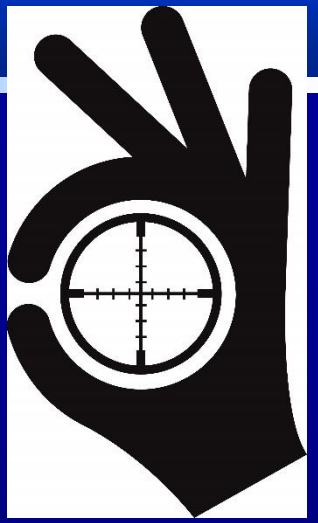
AVERT Study : σχεδιασμός



MRI was performed at Months 0, 6, 12, 18, and 24

*Randomization stratified by corticosteroid use at baseline; † Or <10 mg/wk MTX for ≤4 weeks and no dose 1 month prior to study

AVERT: ασθενείς σε ΥΦΕΣΗ (!)



Error bars represent 95% CI
ITT population

Θεραπεία και όχι καταστολή νόσου

AVERT is the

first study

to demonstrate that

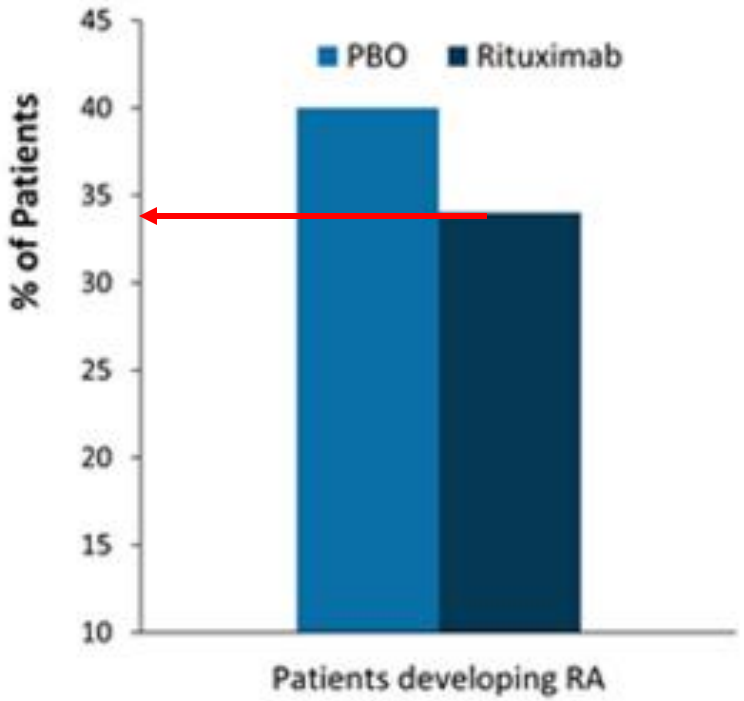
remission can be maintained

after rapid withdrawal of all therapy

(including csDMARDs, biological DMARDS and corticosteroids) in patients with early RA

ΠΡΟΛΗΨΗ (RF & ACPA +)

Prevention of RA by B-Cell-Directed Therapy in the Earliest Phase of the Disease: The PRAIRI Study



- 82 patients with arthralgia who never had clinically manifest arthritis and never used disease-modifying anti-rheumatic drugs were included in a multicenter, randomized, double-blind, placebo-controlled clinical trial
- Risk for development of arthritis in the placebo group was 40%; this risk was reduced by 53% in the rituximab group at 18 months follow up

Gerlag D, et al. EULAR 2016. Abstract OP0182.

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Arthritis Research & Therapy

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RESEARCH ARTICLE | OPEN ACCESS

Two-year results of disease activity score (DAS)-remission-steered treatment strategies aiming at drug-free remission in early arthritis patients (the IMPROVED-study)

Lotte Heimans†, Gülşah Akdemir†, Kirsten V. C. Wevers-de Boer, Yvonne P. Goekoop-Ruiterman, Esmeralda T. Molenaar, Johannes H. L. M. van Groenendael, Andreas J. Peeters, Gerda M. Steup-Beekman, Leroy R. Lard, Peter B. J. de Sonnaville, Bernard A. M. Grillet, Tom W. J. Huizinga and Cornelia F. Allaart

† Contributed equally

Arthritis Research & Therapy 2016 **18**:23 | **DOI:** 10.1186/s13075-015-0912-y

Received: 22 September 2015 | **Accepted:** 29 December 2015 | **Published:** 21 January 2016

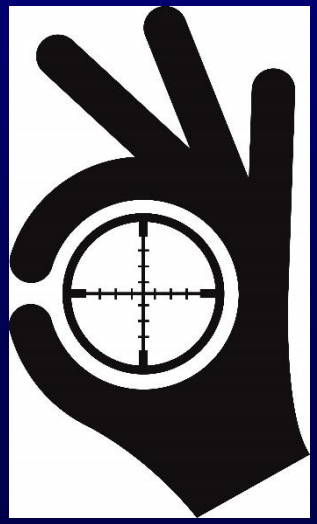
- 610 ασθενείς με πρώιμη ΡΑ ή αδιαφοροποίητη αρθρίτιδα αντιμετωπίσθηκαν με MTX και στοχευμένα υψηλή δόση κορτιζόνης

- Σε ασθενείς **πρώιμα σε ύφεση** (DAS < 1,6 σε 4 μήνες), γινόταν προοδευτικά μείωση και **διακοπή** της αγωγής

- Ασθενείς που **δεν πέτυχαν πρώιμα ύφεση** , τυχαιοποιήθηκαν σε
  - συνδυαστική θεραπεία (MTX & SSZ & HCQ & κορτιζόνη) ή σε
  - MTX & adalimumab
  - Σε DAS<1,6, η αγωγή σταδιακά μειωνόταν και **σταματούσε**

- Στα 2 χρόνια,
  - 301/610 (49 %) ασθενείς ήταν σε DAS-ύφεση και
  - 131/610 (**21 %) ελεύθεροι κάθε αγωγής**

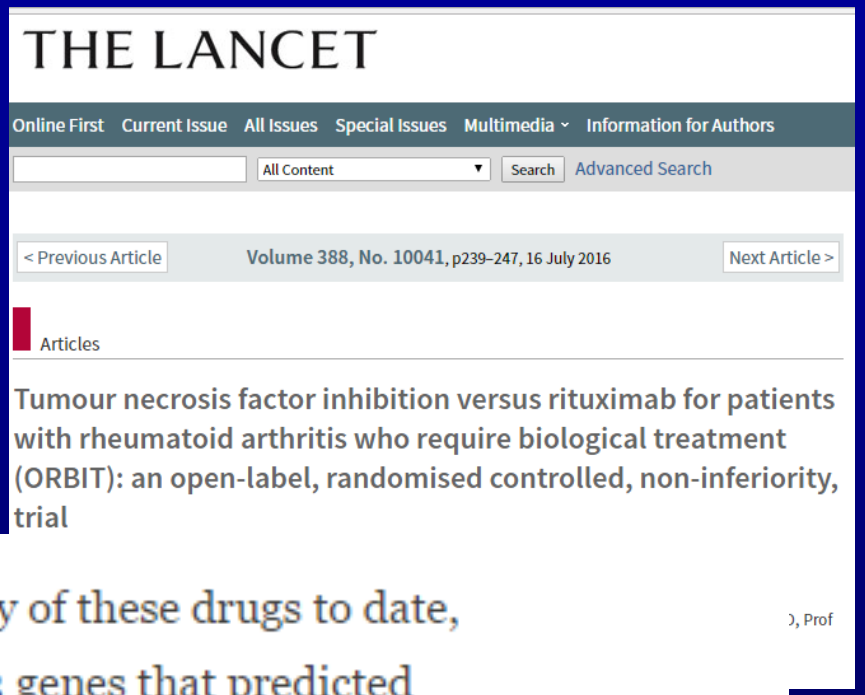
- Ειδικά στην ομάδα **πρώιμης ύφεσης**,
  - 62 % ήταν σε DAS-ύφεση και
  - **29 % ελεύθεροι κάθε αγωγής**



Ανεκπλήρωτες ανάγκες στην PA / κλινικοί

Biomarkers

- Ποιος δεν θα απαντήσει στη θεραπεία / σε κάθε θεραπεία ?
- Σε ποιον μπορεί εύκολα να διακοπεί μια βιολογική θεραπεία ?



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Articles

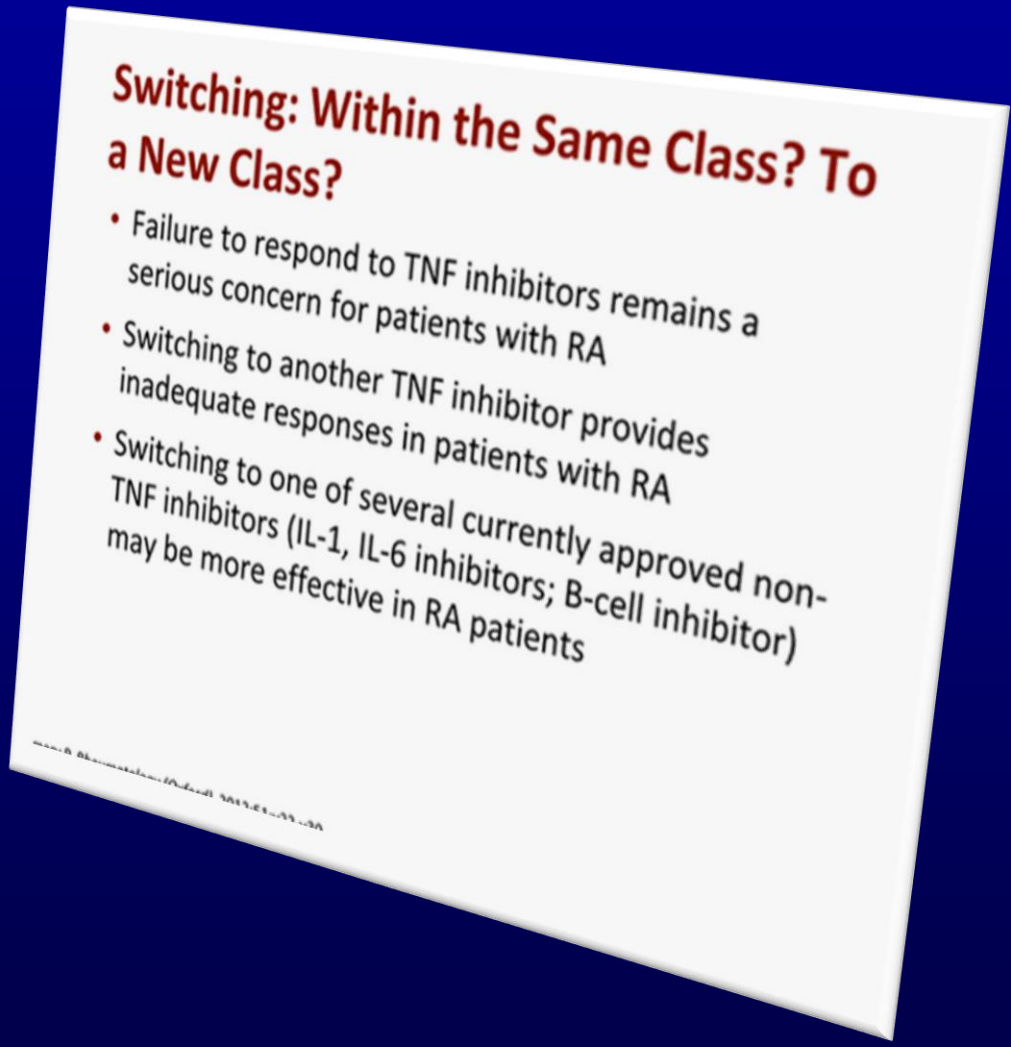
Tumour necrosis factor inhibition versus rituximab for patients with rheumatoid arthritis who require biological treatment (ORBIT): an open-label, randomised controlled, non-inferiority, trial

In the largest gene-expression study of these drugs to date, researchers from Glasgow found 23 genes that predicted response to TNF inhibitors, and 23 more that predicted response to rituximab. They also found eight genes that predicted positive response to both types of drugs.

Ανεκπλήρωτες ανάγκες στην PA / κλινικοί

Θεραπεία ανθεκτικών σε 1ο βιολογικό !

- Δύσκολοι ασθενείς
- Ίδιο ή άλλο μηχανισμό δράσης ?
- Βιολογικό ή αναστ κινασών



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Articles

Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial

Prof Gerd R Burmester, MD, Ricardo Blanco, MD, Christina Charles-Schoeman, MD, Prof Jürgen Wollenhaupt, MD, Cristiano Zerbini, MD, Birgitta Benda, MD, David Gruben, PhD, Gene Wallenstein, PhD, Sriram Krishnaswami, PhD, Samuel H Zwillich, MD, Tamas Koncz, MD, Koshika Soma, MD, John Bradley, MD, Charles Mebus, PhD, on behalf of the ORAL Step investigators

Published: 05 January 2013

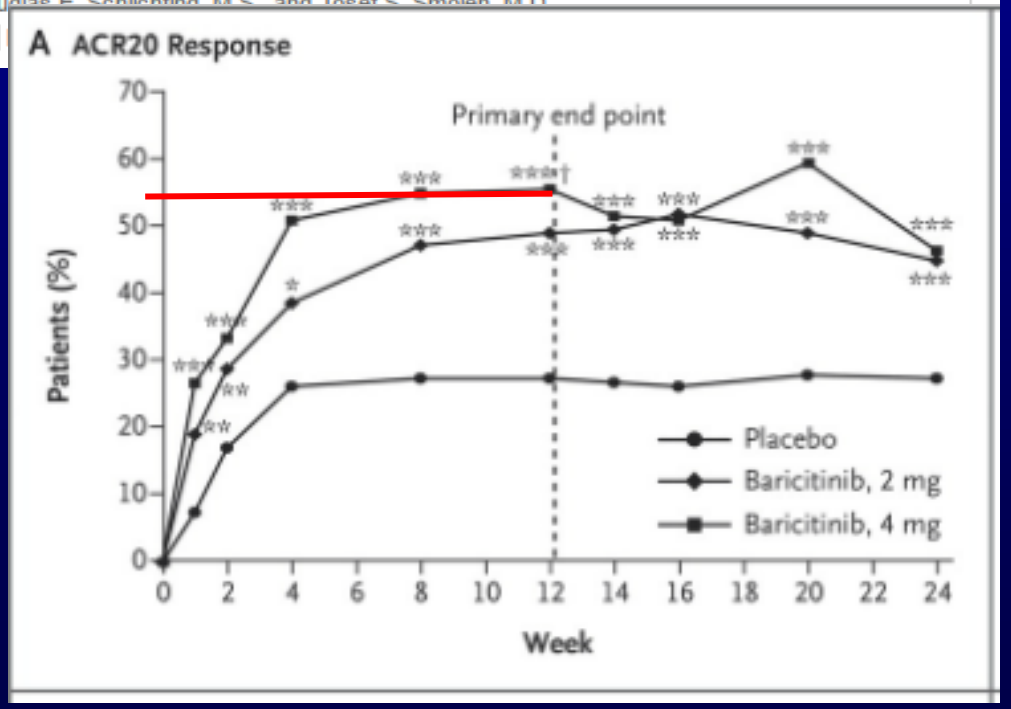
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Baricitinib in Patients with Refractory Rheumatoid Arthritis

Mark C. Genovese, M.D., Joel Kremer, M.D., Omid Zamani, M.D., Charles Ludivico, M.D., Marek Krogulec, M.D., Li Xie, M.S., Scott D. Beattie, Ph.D., Alisa E. Koch, M.D., Tracy E. Cardillo, M.S., Terence P. Rooney, M.D., William L. Macias, M.D., Ph.D., Stephanie de Bono, M.D., Ph.D., Douglas E. Schlichting, M.S., and Josef S. Smolen, M.D.

N Engl J Med 2016; 374:1243-1252



Ανεκπλήρωτες ανάγκες στην ΡΑ καθημέρα κλ πράξη

Έχει νόημα να μετρούμε **επίπεδα φαρμάκου ή ADA** σε ασθενείς που δεν ανταποκρίνονται καλά ?

Επιθετική Θεραπεία επαγωγής ύφεσης τύπου ΣΕΛ

- ΜΤΧ & βιολογικός στην αρχή
- Διατήρηση ύφεσης με ΜΤΧ

Αποκλιμάκωση στεροειδών μετά από επαγωγή ύφεσης (bridging therapy)

Αποκλιμάκωση ΜΤΧ σε ηπατική τοξικότητα

ΧΕΙΡΙΣΜΟΣ ΕΞΑΡΣΗΣ : 1ωση κορτιζόνη με/χωρις αύξηση DMARDS

Ανεκπλήρωτες ανάγκες στην PA / ασθενείς

RHEUMATOLOGY

53, 263, 300

doi:10.1093/rheumatology/keu398

Original article

Quality of life and unmet needs in patients with inflammatory arthropathies: results from the multicentre, observational RAPSODIA study

Roberto Giacomelli[1], Roberto Gorla[2], Francesco Trotta[3], Rosella Tirri[4], Walter Grassi[5], Laura Bazzichi[6], Mauro Galeazzi[7], Marco Matucci-Cerinic[8], Raffaele Scarpa[9], Fabrizio Cantini[10], Roberto Gerli[11], Giovanni Lapadula[12], Luigi Sinigaglia[13], Gianfranco Ferraccioli[14], Ignazio Olivieri[15], Piero Ruscitti[1] and Piercarlo Sarzi-Puttini[16]

Rheumatology Advance Access published October 6, 2014
RHEUMATOLOGY 53, 263, 300
Original article doi:10.1093/rheumatology/keu398

Quality of life and unmet needs in patients with inflammatory arthropathies: results from the multicentre, observational RAPSODIA study

Roberto Giacomelli[1], Roberto Gorla[2], Francesco Trotta[3], Rosella Tirri[4], Walter Grassi[5], Laura Bazzichi[6], Mauro Galeazzi[7], Marco Matucci-Cerinic[8], Raffaele Scarpa[9], Fabrizio Cantini[10], Roberto Gerli[11], Giovanni Lapadula[12], Luigi Sinigaglia[13], Gianfranco Ferraccioli[14], Ignazio Olivieri[15], Piero Ruscitti[1] and Piercarlo Sarzi-Puttini[16]

743 patients with RA, AS and PsA

- their involvement in medical decisions
- quality of life and
- unmet needs

15 years after the introduction of biologic therapies in Italy

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98% of patients reported that their health care practitioner used understandable terms to **explain their condition**

Joint issues and general symptoms (e.g. fatigue and malaise) were common (50%)

All measures of disease activity and self-efficacy scores were markedly **better in patients receiving biologic** vs conventional therapy

Biologic therapy recipients were more **productive at work**

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About 60% of enrolled patients needed **more information**, especially about

diagnosis, medication, exercises and how to improve performance of daily activities

only about one-third (37.1%) were **satisfied with the information** provided during treatment

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Other symptoms were

- tender and swollen joints (52%)
- reduced joint mobility (26%)
- back pain (26%)
- walking difficulties (22%)
- morning stiffness (19%)

ΔΙΑΚΡΙΣΗ:

- ΠΡΩΙΜΗΣ ΡΑ
- ΕΓΚΑΤΕΣΤΗΜΕΝΗΣ ΡΑ
  - Χρόνιες βλάβες (μη αναστρ)
  - Κεντρική ευαισθητοποίηση

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- 72% felt that their life was **ruled by the disease** and expressed frustration about their disability

- More than 60% were **no longer able to carry out normal activities**, which strongly affected their psychological well-being.
  - anxiety was reported by 57% of patients
  - 39% showed levels of irritability
  - 21% reported sexual problems

The unmet need in rheumatology: reports from the Targeted Therapies meeting 2016

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	Primary Unmet Need	Secondary Unmet Needs
Translational science	Understanding the role of the microbiome in disease development and modulation	Identifying sites beyond the joint (*e.g.* gut) that may be driving joint inflammation
	Development of molecular definitions of disease remission, flare, refractoriness	Development of animal models that better reflect human disease
	Identifying Biomarkers including imaging that predict or rapidly identify treatment response	
	Further development of longitudinal, clinically well-characterised cohorts with appropriate imaging, tissue and fluid samples	

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	Primary Unmet Need	Secondary Unmet Needs
Clinical science and therapeutic trials	Development of therapeutics that repair damage, including outside the joint (*e.g.* interstitial lung disease)	Development of therapeutic alternatives for analgesia
	Evaluation of existing therapies in combination	Development of non-immunosuppressive disease control
	Trials that include older patients with comorbidities that will enhance our understanding of the safety of existing therapies	Clinical Study of extreme phenotypes: those who respond very well *vs.* those who don't respond at all
	Trials evaluating the benefits of early treatment (*e.g.* change the long-term prognosis of disease)	Better understanding of secondary failure (anti-drug antibody or other mechanisms)
	The development of approaches to prevent RA (*e.g.* screening, tolerisation, vaccination)	Better understanding and categorisation of seronegative patients
		Development of infrastructure for using electronic health records in clinical research

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	Primary Unmet Need	Secondary Unmet Needs
Clinical care	Achieving cure Identifying patients who can taper their treatment Moderation of drug pricing and the improvement of access to existing and new therapies	Achieving remission in greater proportions of patients (still not more than 30%)

- Hepatitis C Virus : $6.5 billion, is expected to peak in 2024 at over $9.1 billion.
- Back Pain: $41 billion annually.
- High Blood Pressure: $47 billion yearly.
- Diabetes: $60 billion per year.
- Osteoarthritis & Joint Problems: $74 billion
- Chronic Obstructive Pulmonary Disease (COPD) and Asthma: $76 billion per year.
- Mental Illness: $83 billion.
- Cancer: $87 billion in 2014
- Injuries & Trauma: annual cost at $92 billion.
- Heart Disease: $100 billion per year.

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ΓΙΑΝΝΕΝΑ ΝΟΕΜΒΡΗΣ 16