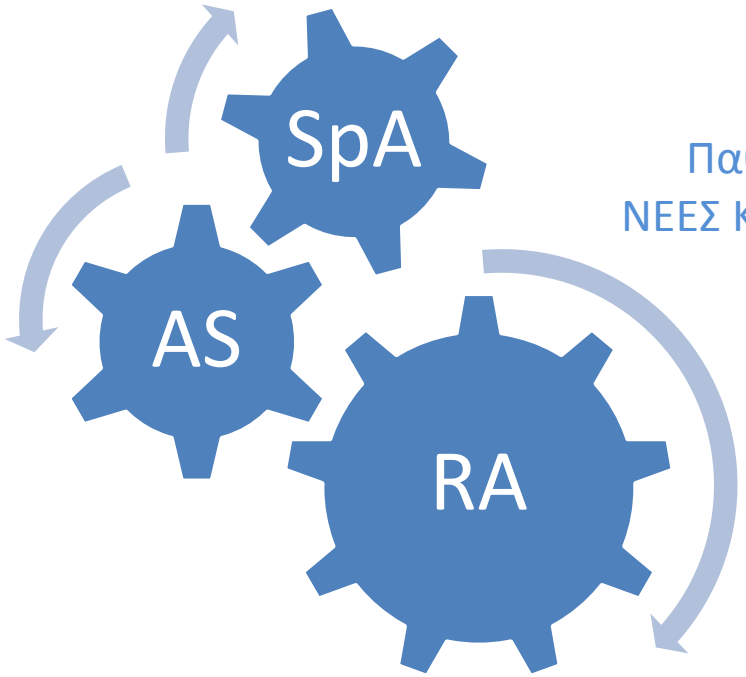
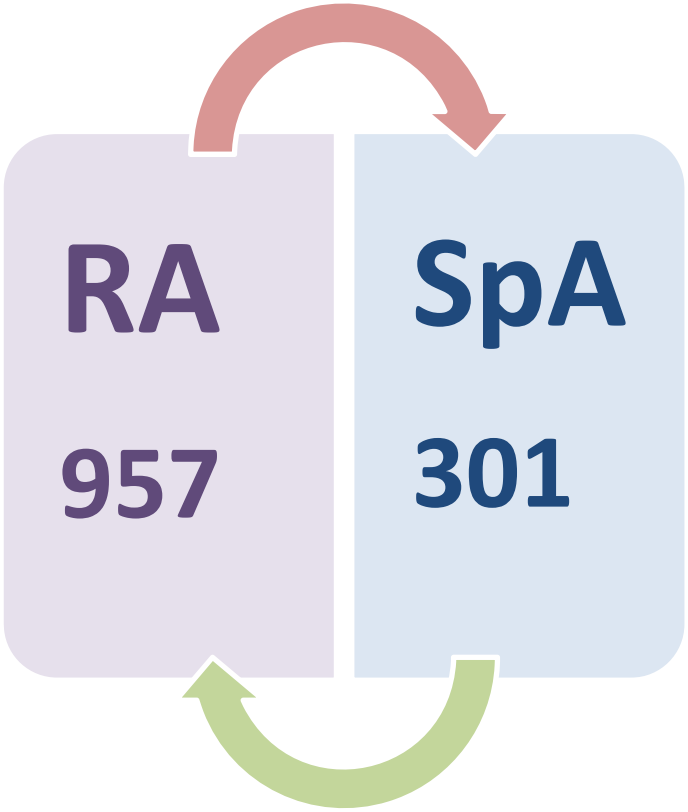
ΦΛΕΓΜΟΝΩΔΕΙΣ ΑΡΘΡΙΤΙΔΕΣ

βιβλιογραφική ενημέρωση



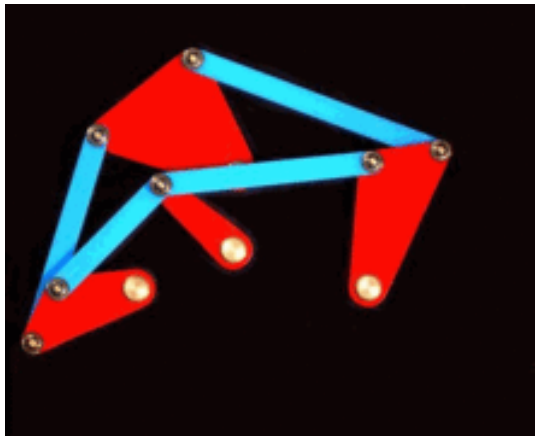
Β. Τζαβάρα
Παθολόγος/Ανοσολόγος
ΝΕΕΣ Κοργιαλένειο-Μπενάκειο

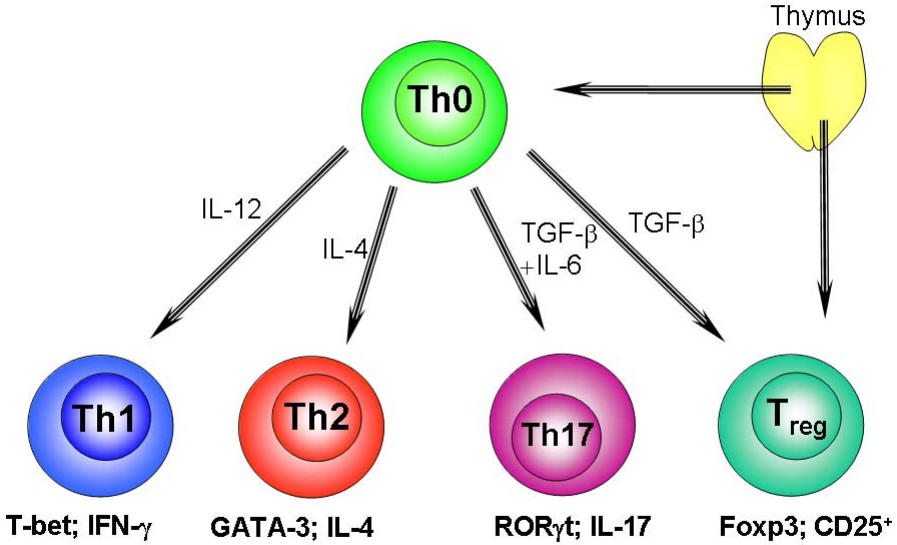
Pubmed
δημοσιεύσεις 2/1/2015-9/10/2015



Οροαρνητικές σπονδυλοαρθροπάθειες

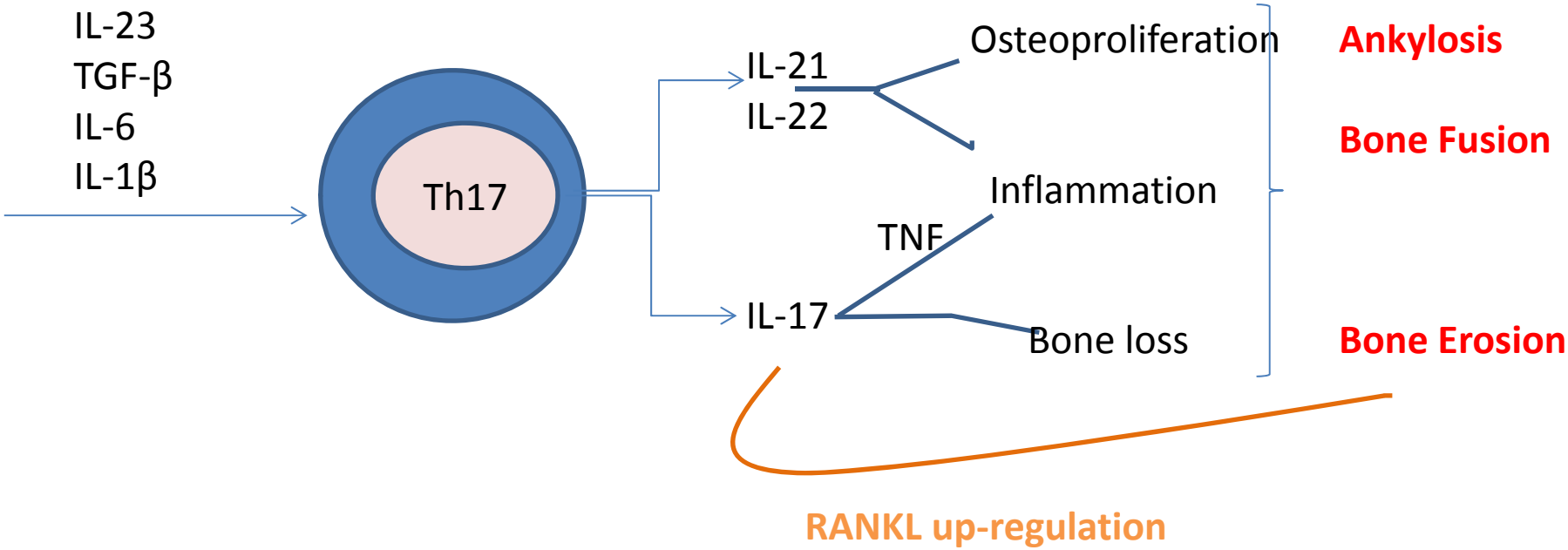
Pathogenesis role of IL-17





The interleukin IL-23/IL-17 axis in ankylosing spondylitis: new advances and potentials for treatment.

Jethwa H[1], Bowness P[1,2]Clin Exp Immunol. 2015 Jun 17. doi: 10.1111/cei.12670.



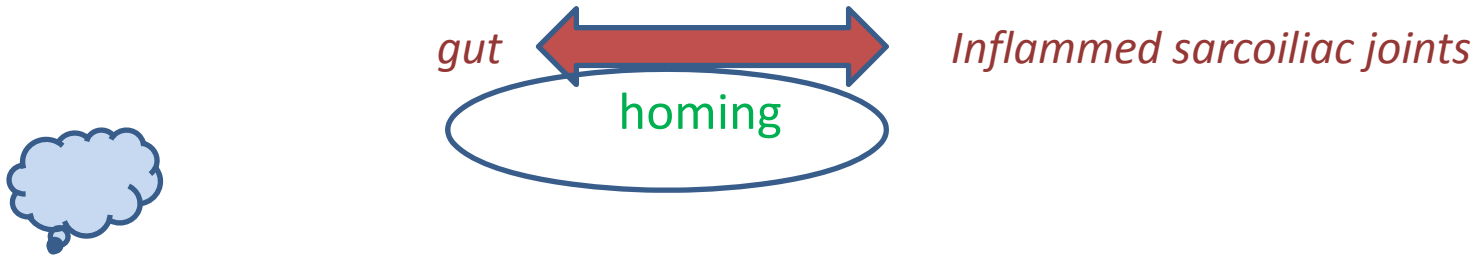
Type 3 innate lymphoid cells producing IL-17 and IL-22 are expanded in the gut, in the peripheral blood, synovial fluid and bone marrow of patients with ankylosing spondylitis. Ciccia F[1], et al Ann Rheum Dis. 2015 Sep;74(9):1739-47

AS

Gut-derived IL-17(+) and IL-22(+) IL-23 responsive innate lymphoid cells

are expanded in
- Peripheral Blood
- Synovial Fluid
- inflammed BM

Increased expression of Vascular Addressin Cell Adhesion Molecule 1(MADCAM-1)



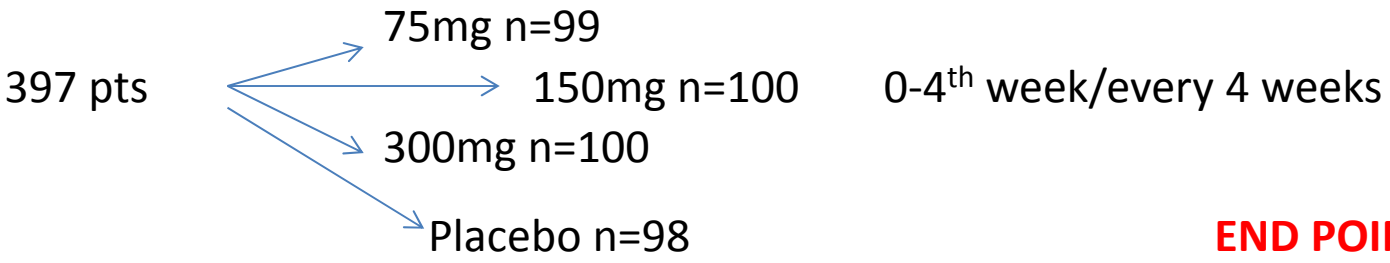
Anti TNFs reduce ILCs-3 in gut and circulation/ reduce MADCAM-1 expression

Blocking IL-17

Lancet. 2015 Jun 26. pii: S0140-6736(15)61134-5. doi: 10.1016/S0140-6736(15)61134-5. [Epub ahead of print]

Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial.

McInnes IB, Mease PJ; FUTURE 2 Study Group



END POINTS at 24 weeks

	300mg	Vs placebo	150mg	Vs placebo	75 mg	Vs placebo
ACR 20	54 (54%)	P<0.0001	51 (51%)	P<0.0001	29 (29%)	P=0.039
ACR 50	35 (35%)	P=0.004	35 (35%)	P=0.004	18 (18%)	p-=0.9

TNF naïve	39/67	P<0.001	40/63	P<0.001	24/65	p-=0.07	ACR 20
	26/67	p<0.001	28/64	P<0.001	16/65	P=0.07	ACR 50
TNF-IR	15/33	P=0.007	11/37	P=0.12	5/34	P=0.9	ACR 20
	9/33	P=0.04	7/37	P=0.12	5/34	P=0.9	ACR 50

στο σύνολο

Resolution of dactylitis	**52/111**	**p=0.91**
Resolution of enthesitis	**76/188**	**p=0.91**

Lancet. 2015 Jun 26. pii: S0140-6736(15)61134-5. doi: 10.1016/S0140-6736(15)61134-5. [Epub ahead of print]

Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial.

SIDE EFFECTS

	300mg	150mg	75mg
infections	79%	82%	64%
upper resiratory infections	18%	18%	22%
nasopharyngitis	13,5	12,5	10,5
diarrhoea, nausea, headacke,sinusitis	<8%		

More frequent Candida infections
No death was reported

Original Article

Secukinumab Inhibition of Interleukin-17A in Patients with Psoriatic Arthritis

Philip J. Mease, M.D., Iain B. McInnes, Ph.D., Bruce Kirkham, M.D., Arthur Kavanaugh, M.D., Proton Rahman, M.D., Désirée van der Heijde, M.D., Ph.D., Robert Landewé, M.D., Ph.D., Peter Nash, M.B., B.S., Luminita Pricop, M.D., Jiacheng Yuan, Ph.D., Hanno B. Richards, M.D., Shephard Mpofu, M.D., for the FUTURE 1 Study Group

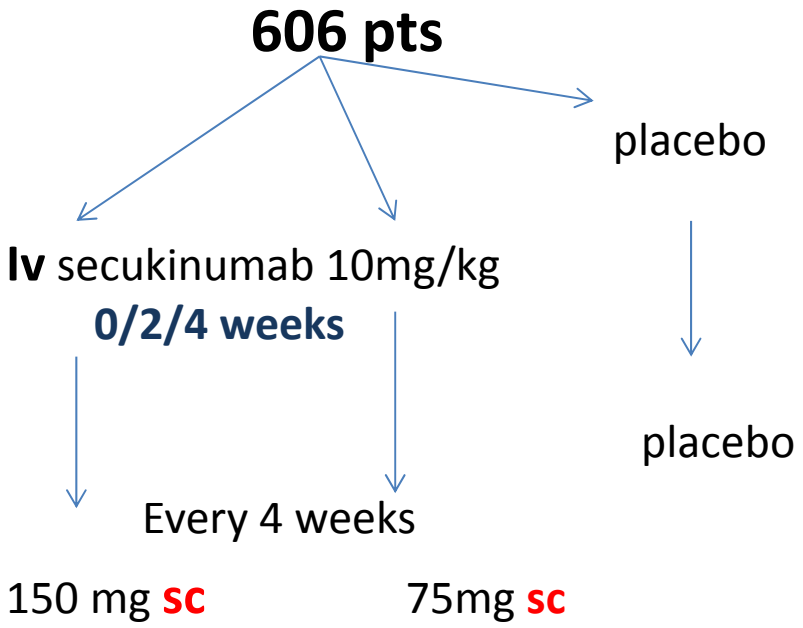
N Engl J Med
Volume 373(14):1329-1339
October 1, 2015

The NEW ENGLAND JOURNAL of MEDICINE

Secukinumab Inhibition of Interleukin-17A in Patients with Psoriatic Arthritis

N Engl J Med
Volume 373(14):1329-1339 October 1, 2015

METHODS



END POINTS

Clinical improvement
at 24 week,
Side effects

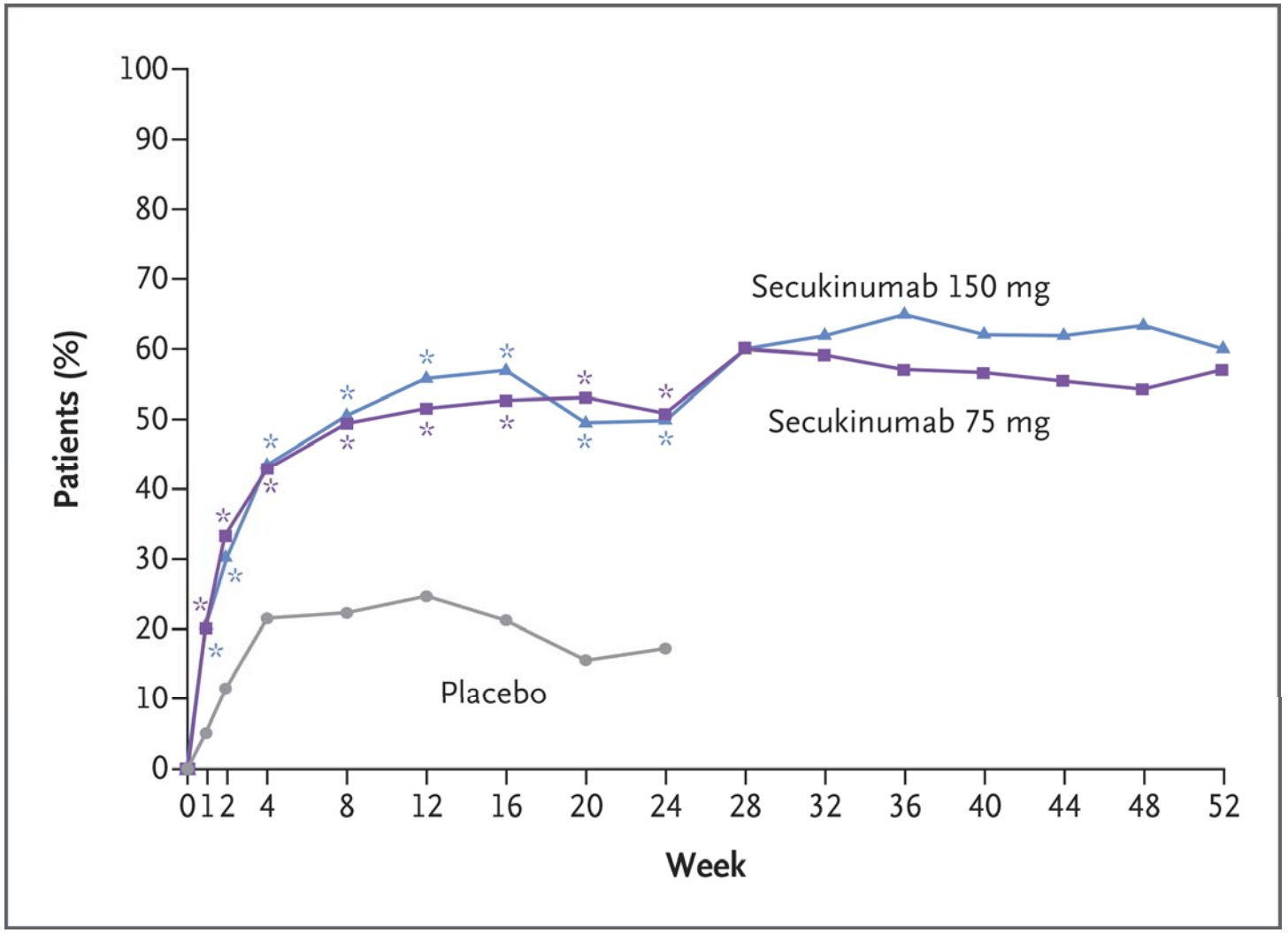


Table 2. Comparison of Efficacy at Week 24 during the Placebo-Controlled Phase.*

Outcome	Secukinumab, 150 mg (N=202)	Secukinumab, 75 mg (N=202)	Placebo (N=202)
ACR20 response: primary end point — no. (%)†	101 (50.0)‡	102 (50.5)‡	35 (17.3)
Prespecified secondary end points			
PASI 75 response — no./total no. (%)§	66/108 (61.1)‡	70/108 (64.8)‡	9/109 (8.3)
PASI 90 response — no./total no. (%)§	49/108 (45.4)‡	53/108 (49.1)‡	4/109 (3.7)
Change from baseline in DAS28-CRP	−1.62±0.08‡	−1.67±0.09‡	−0.77±0.12
Change from baseline in SF-36 physical component summary	5.91±0.53‡	5.41±0.52‡	1.82±0.72
Change from baseline in disability assessment (HAQ-DI score)	−0.40±0.04‡	−0.41±0.04‡	−0.17±0.05
ACR50 response — no. (%)	70 (34.7)‡	62 (30.7)‡	15 (7.4)
Change from baseline in joint structural damage (mTSS score)¶	0.13±0.09‖	0.02±0.12‖	0.57±0.19
Patients with resolution of dactylitis — no./total no. (%)**	109/208 (52.4)‖		18/116 (15.5)
Patients with resolution of enthesitis — no./total no. (%)**	121/255 (47.5)‖		15/117 (12.8)

* Plus–minus values are means ±SE. The change from baseline in the DAS28-CRP and the SF-36 physical component summary were calculated as least-squares means in inferential analysis. Prespecified primary and secondary end points were analyzed according to a statistical hierarchy. End points are shown in the order of testing, except the effect of individual doses of secukinumab on joint structural damage, which was tested after dactylitis and enthesitis end points.

† The primary end point was an improvement of at least 20% in the American College of Rheumatology response criteria (ACR20 response).

‡ $P<0.001$ for the comparison with placebo.

§ PASI 75 and PASI 90 denote improvements of 75% and 90%, respectively, in the score on the psoriasis area-and-severity index.

¶ Joint structural damage was measured by means of the van der Heijde–modified total Sharp score (mTSS). Data are shown for 185 patients who received 150 mg of secukinumab, 181 patients who received 75 mg of secukinumab, and 179 patients who received placebo. For the pooled secukinumab groups, the mean change from baseline in the mTSS score was 0.08±0.07 ($P=0.01$).

‖ $P<0.05$ for the comparison with placebo.

** For this analysis, data for the two secukinumab groups were pooled.

Table 3. Adverse Events through Week 16 (Placebo-Controlled Period) and the Entire Safety-Data Period.*

Variable	Through Week 16 (Placebo-Controlled Period)†				Entire Safety-Data Period		
	Secukinumab, 150 mg (N=202)	Secukinumab, 75 mg (N=202)	Any Secukinumab (N=404)	Placebo (N=202)	Secukinumab, 150 mg (N=295)	Secukinumab, 75 mg (N=292)	Any Secukinumab (N=587)
	no. of patients (%)				*no. of patients (no. of events/100 patient-yr)*		
Any adverse event	131 (64.9)	122 (60.4)	253 (62.6)	118 (58.4)	243 (229.0)	228 (183.2)	471 (204.3)
Any serious adverse event‡	9 (4.5)	5 (2.5)	14 (3.5)	10 (5.0)	38 (11.5)	25 (7.4)	63 (9.4)
Myocardial infarction	0	0	0	0	1 (0.3)	1 (0.3)	2 (0.3)
Stroke	0	1 (0.5)	1 (0.2)	0	0	4 (1.1)	4 (0.6)
Death	0	0	0	0	0	1	1
Discontinuation of study treatment owing to any adverse event§	3 (1.5)	4 (2.0)	7 (1.7)	5 (2.5)	10 (3.4)‡	13 (4.5)‡	23 (3.9)‡
Infection or infestation	67 (33.2)	53 (26.2)	120 (29.7)	47 (23.3)	166 (81.8)	159 (71.3)	325 (76.3)
Candida infection	2 (1.0)	1 (0.5)	3 (0.7)	0	6 (1.7)	4 (1.2)	10 (1.4)
Common adverse events¶							
Nasopharyngitis	19 (9.4)	14 (6.9)	33 (8.2)	9 (4.5)	46 (14.8)	54 (17.8)	100 (16.3)
Headache	11 (5.4)	11 (5.4)	22 (5.4)	6 (3.0)	23 (6.9)	25 (7.7)	48 (7.3)
Upper respiratory tract infection	13 (6.4)	9 (4.5)	22 (5.4)	10 (5.0)	49 (15.5)	43 (13.4)	92 (14.5)
Hypercholesterolemia	6 (3.0)	8 (4.0)	14 (3.5)	5 (2.5)	9 (2.6)	11 (3.3)	20 (2.9)
Diarrhea	6 (3.0)	4 (2.0)	10 (2.5)	6 (3.0)	17 (5.0)	13 (3.8)	30 (4.4)
Hypertension	3 (1.5)	7 (3.5)	10 (2.5)	5 (2.5)	13 (3.8)	19 (5.7)	32 (4.7)
Nausea	4 (2.0)	5 (2.5)	9 (2.2)	2 (1.0)	7 (2.0)	13 (3.8)	20 (2.9)
Back pain	3 (1.5)	5 (2.5)	8 (2.0)	2 (1.0)	17 (5.0)	23 (6.9)	40 (5.9)

* During the placebo-controlled period, the mean (±SD) exposure to a study drug was 113.0±16.1 days in the group receiving 150 mg of secukinumab, 112.3±15.6 days in the group receiving 75 mg of secukinumab, and 110.3±14.6 days in the group receiving placebo. The safety-data period was defined as the period from baseline through the week 52 visit of the last patient (maximum secukinumab exposure, 103 weeks; mean and median exposure, 438.5 days and 456 days, respectively). In the analysis of the entire study period, the secukinumab groups include any patients who received the stated dose of secukinumab and those who were randomly assigned to the placebo group at baseline and who underwent a second randomization to active treatment at week 16 or 24.

† In the efficacy analyses, the placebo-controlled period included data through week 24, with imputation for patients who switched to active treatment at week 16. In the safety analyses, the placebo-controlled period included data only through week 16, when patients received the originally assigned study medication.

‡ A list of the most common serious adverse events is provided in Table S3 in the Supplementary Appendix.

§ Exposure-adjusted incidence rates were not calculated for study-drug discontinuations owing to adverse events. Percentages are shown, as indicated.

¶ The most common adverse events, which are expressed according to the preferred terms in the *Medical Dictionary for Regulatory Activities*, were reported in at least 2% of patients in the pooled secukinumab groups through week 16.

Mease PJ et al. N Engl J Med 2015;373:1329-1339.

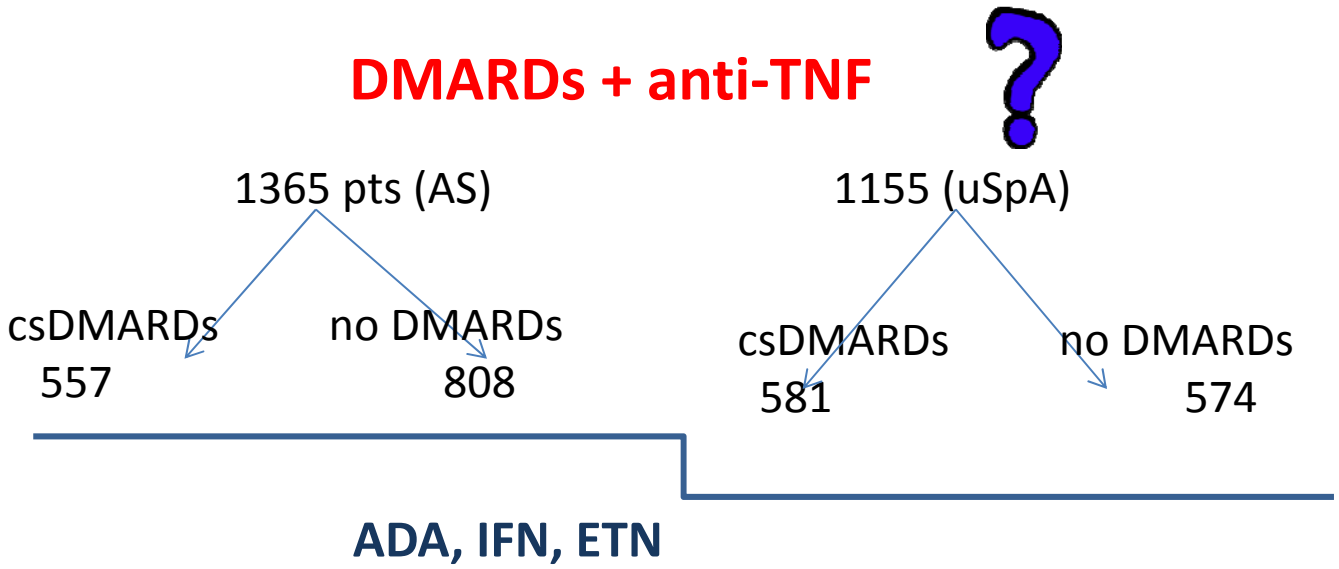
- **Secukinumab was more effective than placebo in patients with psoriatic arthritis, which validates interleukin-17A as a therapeutic target.**
- **Infections were more common in the secukinumab groups than in the placebo group.**
- **The study was neither large enough nor long enough to evaluate uncommon serious adverse events or the risks associated with long-term use**.

The NEW ENGLAND JOURNAL of MEDICINE

The effect of comedication with conventional synthetic disease modifying antirheumatic drugs on TNF inhibitor drug survival in patients with ankylosing spondylitis and undifferentiated spondyloarthritis: results from a nationwide prospective study.

Lie E[1], et al ARTIS Study Group

Ann Rheum Dis. 2015 Jun;74(6):970-8. doi: 10.1136/annrheumdis-2014-206616. Epub 2015 Feb



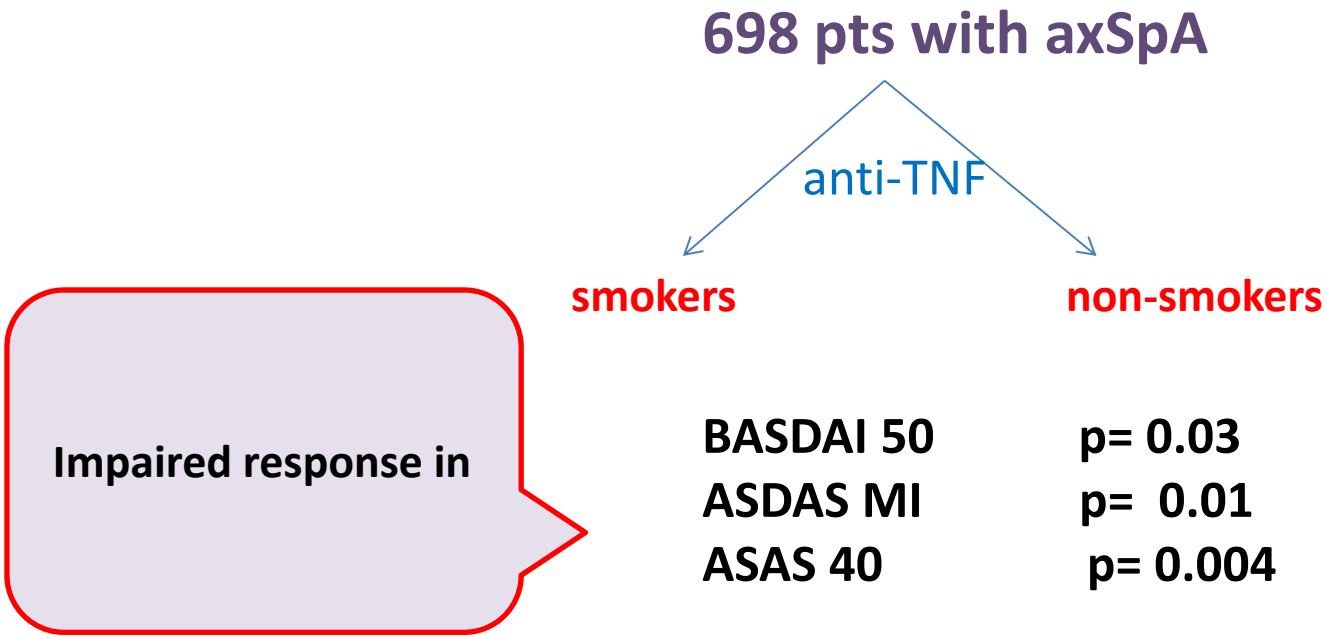
Cox regression:

better retention to TNF therapy **AS (p<0.0010)**

uSpA (p=0.020)

Impaired response to treatment with tumor necrosis factor a inhibitors in smokers with axial spondyloarthritis

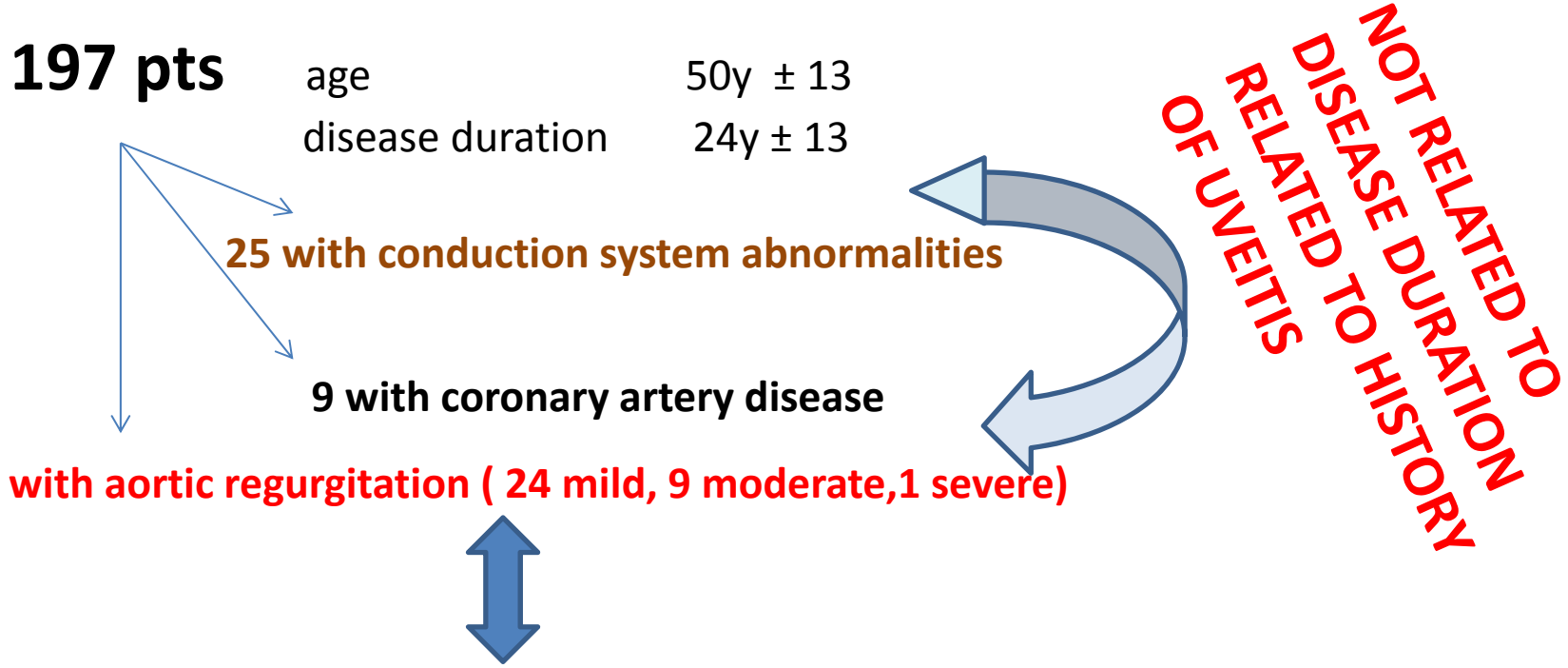
Ann Rheum Dis 2015 Feb 9 Ciurea A et al



Am J Med. 2015 Jun 4. pii: S0002-9343(15)00443-X. doi: 10.1016/j.amjmed.2015.04.032. [Epub ahead of print]

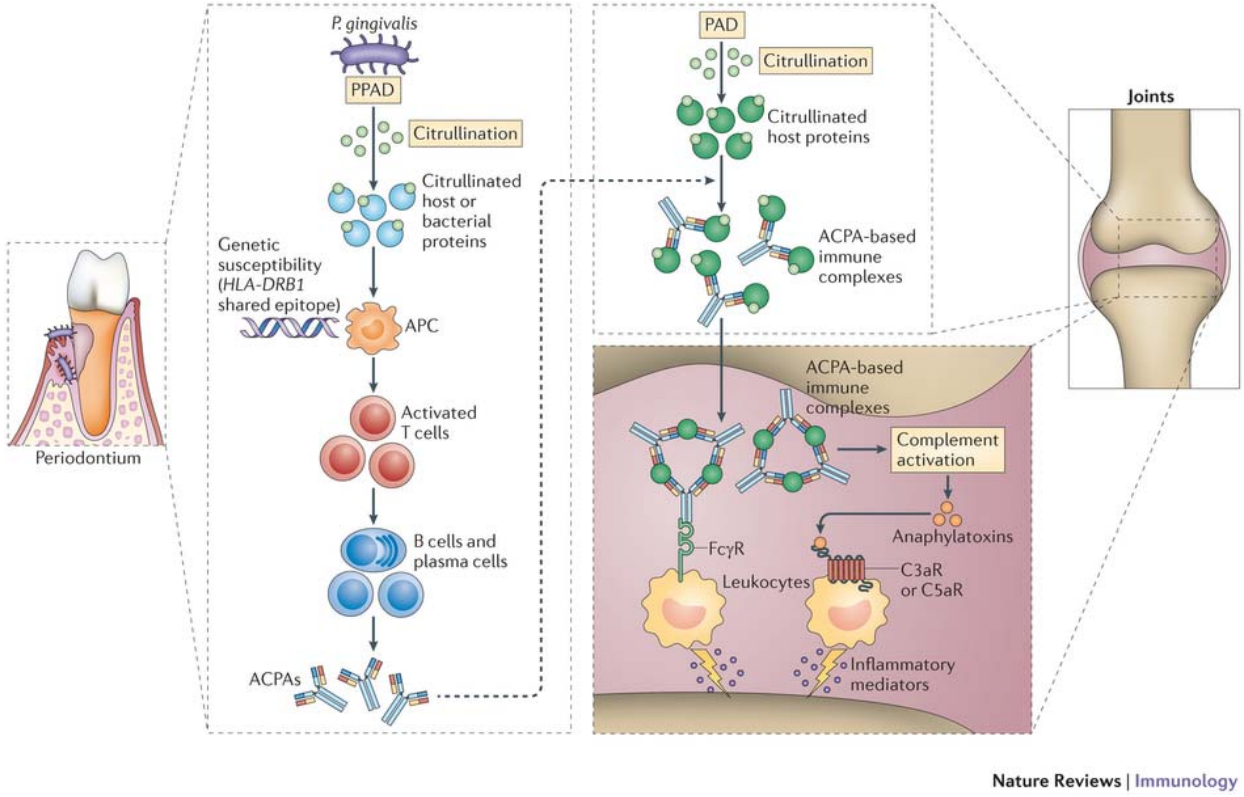
Aortic Regurgitation Is Common in Ankylosing Spondylitis: Time for Routine Echocardiography Evaluation?

Klingberg E[1], Sveälv BG[2], Täng MS[2], Bech-Hanssen O[2], Forsblad-d'Elia H[1], Bergfeldt L[3]



RA

παθοφυσιολογία



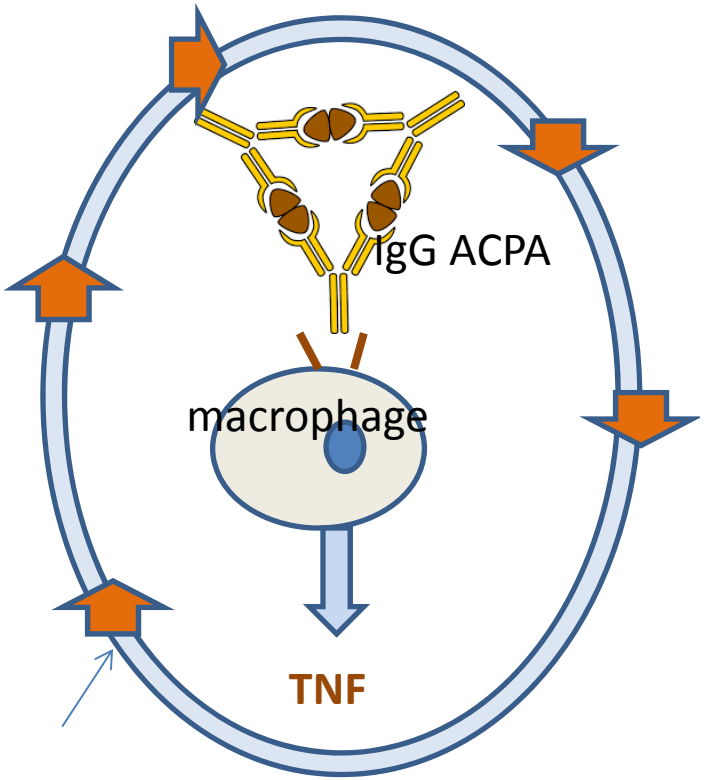
IgM rheumatoid factor amplifies the inflammatory response of macrophages induced by the rheumatoid arthritis-specific immune complexes containing anticitrullinated protein antibodies.

Laurent L, et al

Ann Rheum Dis. 2015 Jul;74(7):1425-31. doi: 10.1136/annrheumdis-2013-204543. Epub 2014 Mar 11.

IgM and IgA rheumatoid factors purified from rheumatoid arthritis sera boost the Fc receptor- and complement-dependent effector functions of the disease-specific anti-citrullinated protein autoantibodies.

Anquetil F 1J Immunol. 2015 Apr 15;194(8):3664-74. doi: 10.4049/jimmunol.1402334. Epub 2015 Mar 13.

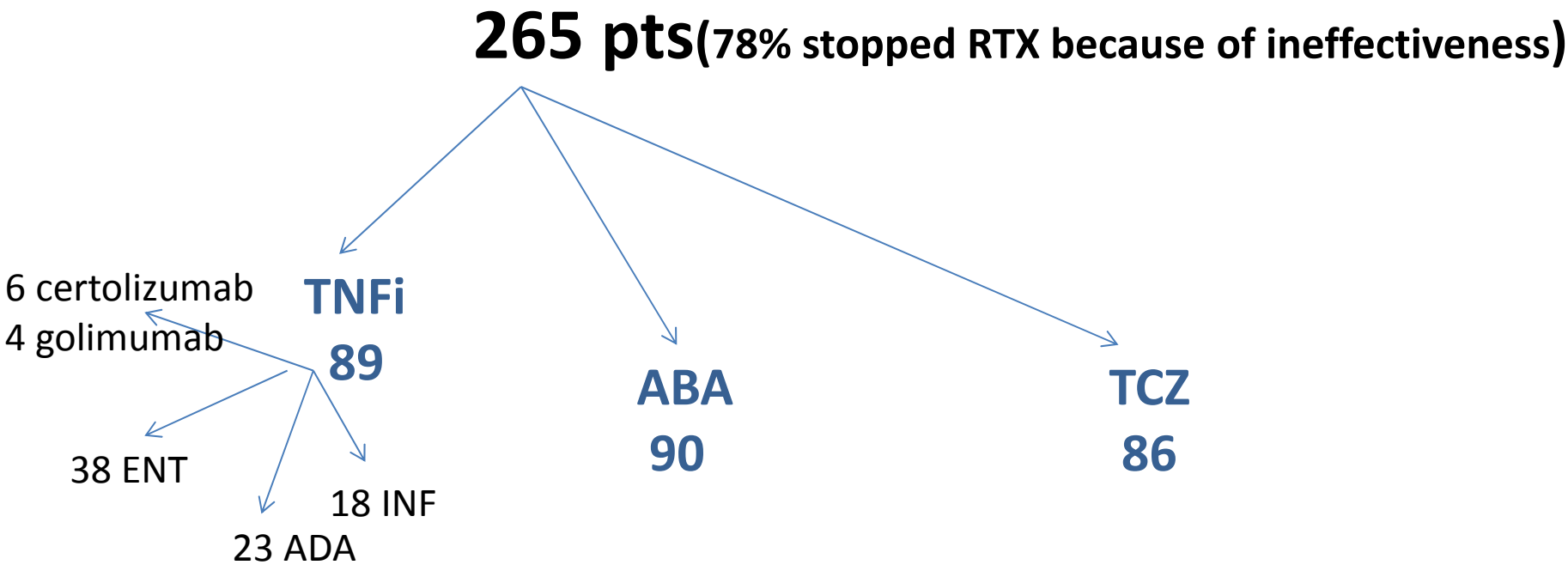


θεραπεία

Rituximab done: what's next in rheumatoid arthritis? A European observational longitudinal study assessing the effectiveness of biologics after rituximab treatment in rheumatoid arthritis

Walker UA et al Rheumatology (Oxford). 2015 Aug 27. pii: kev297. [Epub ahead of print]

OBJECTIVE effectiveness of biologics after RTX treatment



Rituximab done: what's next in rheumatoid arthritis? A European observational longitudinal study assessing the effectiveness of biologics after rituximab treatment in rheumatoid arthritis

	All	TNFi	ABA	TCZ	p
Age	55±12,2	56±12,3	55±12	53,2±12	
RA duration	7-17	5-19	8-17	7-17	0.9
RF (+) %	72,6	70,2	72,4	75,2	0.77
antiCCP (+) %	73,6	68,4	78,8	74,3	0,61
No bDMARDS prior RTX 0 1 2 ≥3	 11,4 25,6 32,9 30,1	 13,5 29,7 32,4 24,3	 17,6 21,6 31,1 71,9	 2,8 25,4 35,2 55,8	0.08
Median prednisone	5-10	5-10	5-10	5-10	
MTX %	63,3	62,9	64	62,8	

Rituximab done: what's next in rheumatoid arthritis?

RESULTS AT 24 WEEKS

	baseline			At 6 months			
DAS28 -ESR %	TNF	ADA	TCZ	TNF	ADA	TCZ	P
remission	0	2,4	6,9	25,5	14,3	62,1	**<0.001**
Low activity	5,1	2,4	0	10,3	2,4	10,3	
Moderate activity	28,2	26,1	24,1	46	45,2	20,7	
High activity	66,7	69,7	69	18	38	6,9	

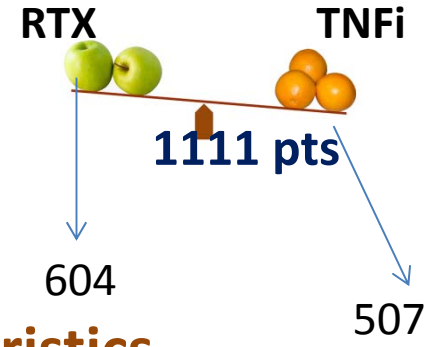
EULAR good response

TNF	ADA	TCZ	P
31%	**14%**	**66%**	**<0.001**

Rituximab versus an alternative TNF inhibitor in patients with rheumatoid arthritis who failed to respond to a single previous TNF inhibitor: SWITCH-RA, a global, observational, comparative effectiveness study

Emery P, et al. Ann Rheum Dis 2015;74:979–984. doi:10.1136/annrheumdis-2013-203993

OBJECTIVES:



inadequate response to previous TNF

Baseline characteristics

	RTX	TNFi	P
Inefficacy	465	362	
MTX	199	180	
Corticosteroids	293	229	
Seropositives RF+ /APCA+	81,7%	70,6%	0,004
DAS28-ESR	5,2	4,8	<0,001

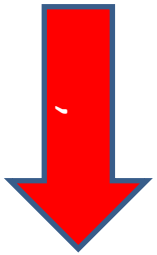
Rituximab versus an alternative TNF inhibitor in patients with rheumatoid arthritis who failed to respond to a single previous TNF inhibitor: SWITCH-RA, a global, observational, comparative effectiveness study

CHANGES IN	DAS 28-ESR AT	6 MONTHS
RTX	TNFi	p
-1,5	-1,1	0,007

	seropositive 559			seronegative 169		
	RTX	TNF	p	RTX	TNF	P
All	-1,6	-1,2	0,011	-1,3	-1,1	0,449
inefficacy	-1,9	-1,5	0,021	-0,5	-0,2	0,47

Rituximab done: what's next in rheumatoid arthritis? A European observational longitudinal study assessing the effectiveness of biologics after rituximab treatment in rheumatoid arthritis

Rituximab versus an alternative TNF inhibitor in patients with rheumatoid arthritis who failed to respond to a single previous TNF inhibitor: SWITCH-RA, a global, observational, comparative effectiveness study



When a bDMARD is proven to be ineffective, maybe is better switching to a biological therapy with a different mode of action

TREATMENT RELATED SIDE EFFECTS

Methotrexate use and risk of lung disease in psoriasis, psoriatic arthritis, and inflammatory bowel disease: systematic literature review and meta-analysis of randomised controlled trials

Conway R, et al BMJ 2015 Mar 13;350

OBJECTIVES: evaluation of the relative risk of pulmonary disease among patients with psoriasis, psoriatic arthritis, and inflammatory bowel disease treated with methotrexate.

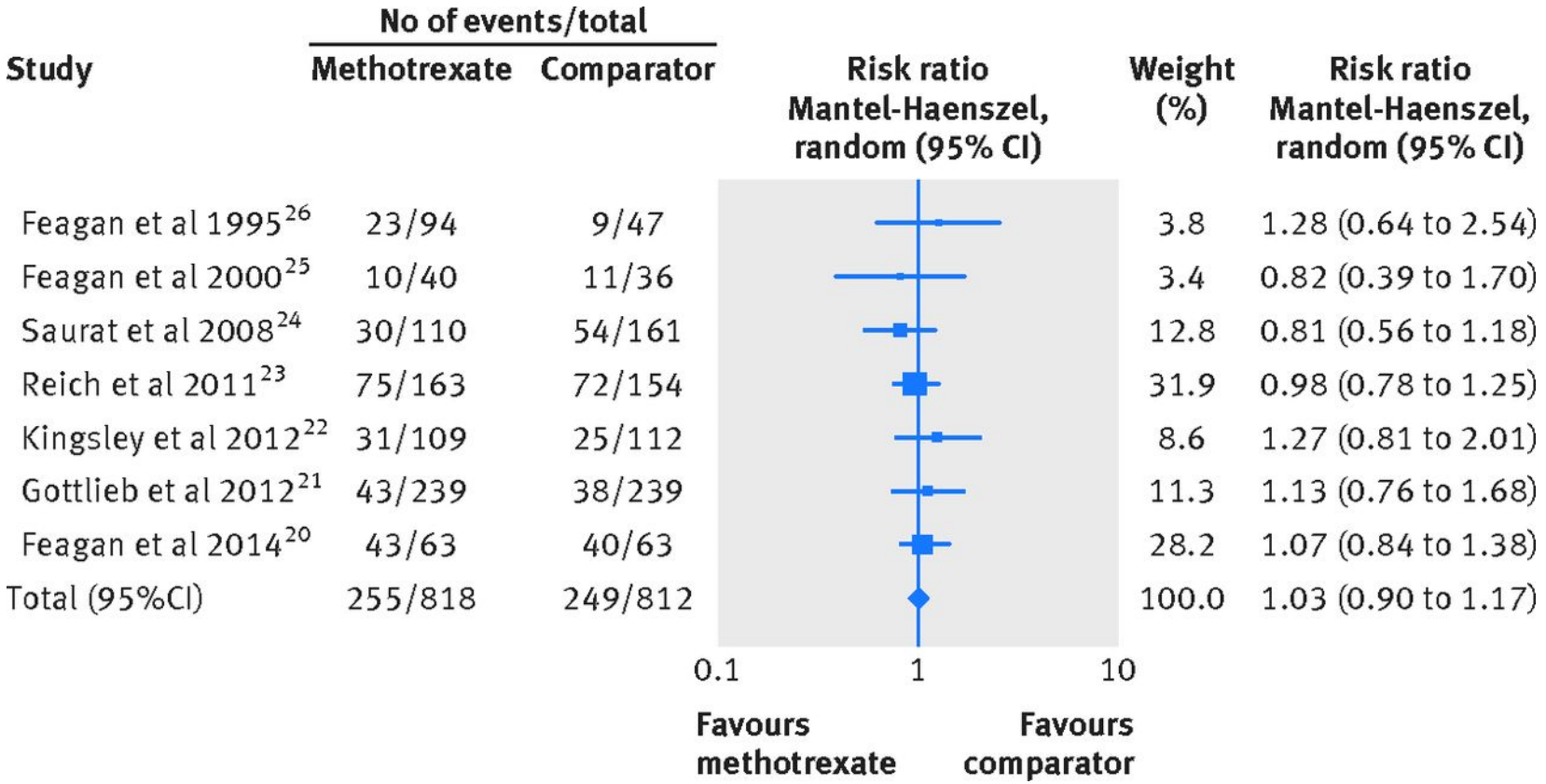
METHODS: 7 double blind randomized control trials of MTX vs placebo reviewed by all authors

RESULTS:

1630 pts

504 adverse respiratory events

RESULTS : Forest plot of relative risk for total adverse respiratory events for methotrexate compared with comparator agents.



CONCLUSIONS:

no increased risk of lung disease in methotrexate treated patients

Frequent conversion of tuberculosis screening tests during anti-tumour necrosis factor therapy in patients with rheumatic diseases. Hatzara C, et al

Ann Rheum Dis. 2015 Oct;74(10):1848-53

OBJECTIVES: determine the rate of TB screening test conversion during anti-TNF therapy

METHODS: prospective study.

Frequent conversion of tuberculosis screening tests during anti-tumour necrosis factor therapy in patients with rheumatic diseases.

METHODS: 70 pts (33 RA, 33 SpA, 4 other)

Baseline screening:

TST<5mm, T-SPOT (-), QuantiFERON TB (-), QFT-GIT (-), chest x-ray

27 ADA 14 ETN 16 INF 8 GOL 5 CERTO/PEGOL

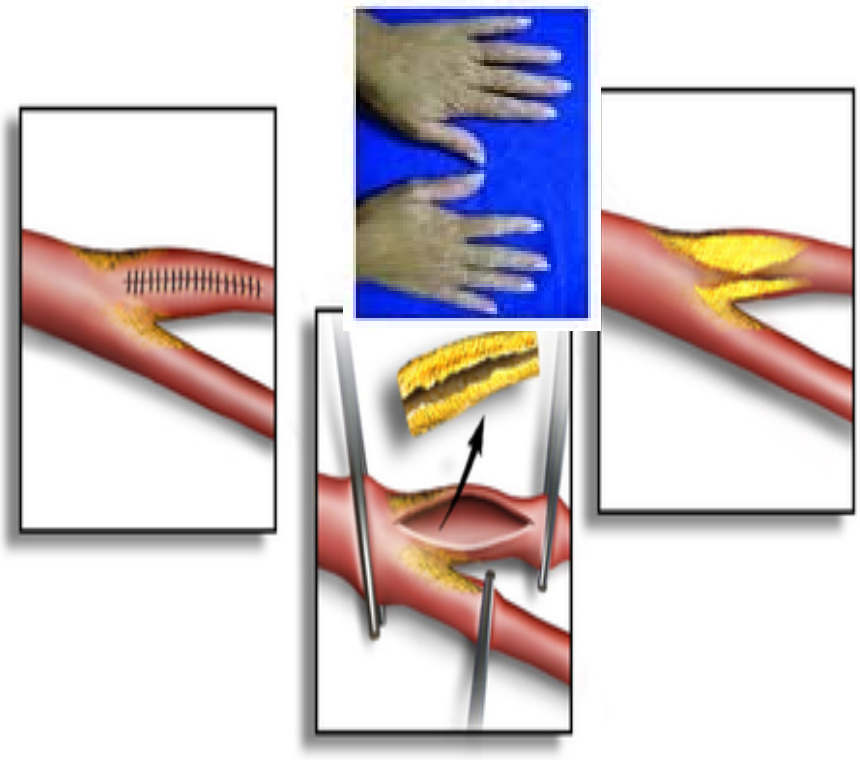
1 year

RESULTS 29% conversion with one screening assay

(13% TST, 10% T-SPOT, 7% GFT_GIT), 40% isoniazid , NO active TB

CONCLUSIONS: re-screening strategies and contemplating latent TB therapy 

COMORBIDITIES

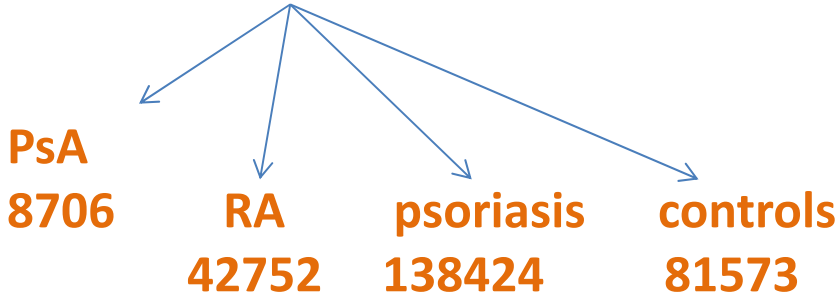


Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study

Ogdie A, et al. Ann Rheum Dis 2015;74:326–332.

Objectives quantify the risk of major adverse cardiovascular events (MACE) in PsA, RA and psoriasis  general population after adjusting for traditional cardiovascular risk factors.

Methods population-based longitudinal cohort study- 1994 - 2010



Conclusions Cardiovascular risk is higher in psoriasis, PsA or RA.

even higher in no-DMARDs population

The age-risk relationship of hematologic malignancies in patients with rheumatoid arthritis: a nationwide retrospective cohort study

Lin YC et al Clin Rheumatol. 2015 Jul;34(7):1195-202.

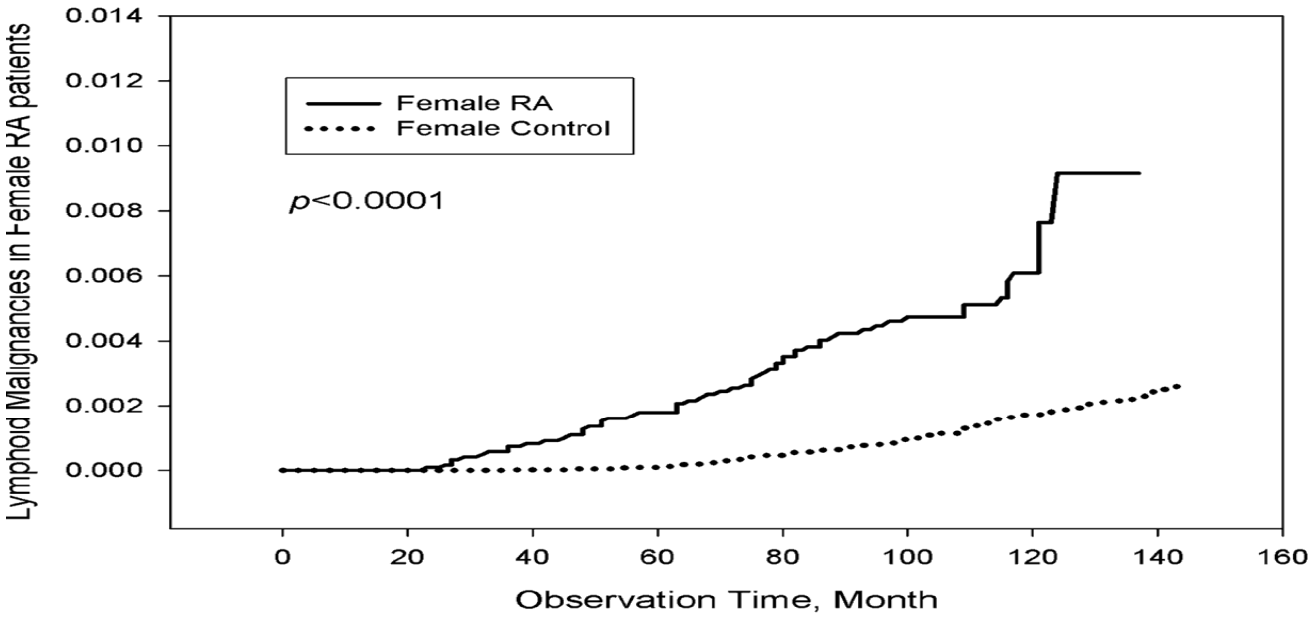
17472 pts **87360 controls**

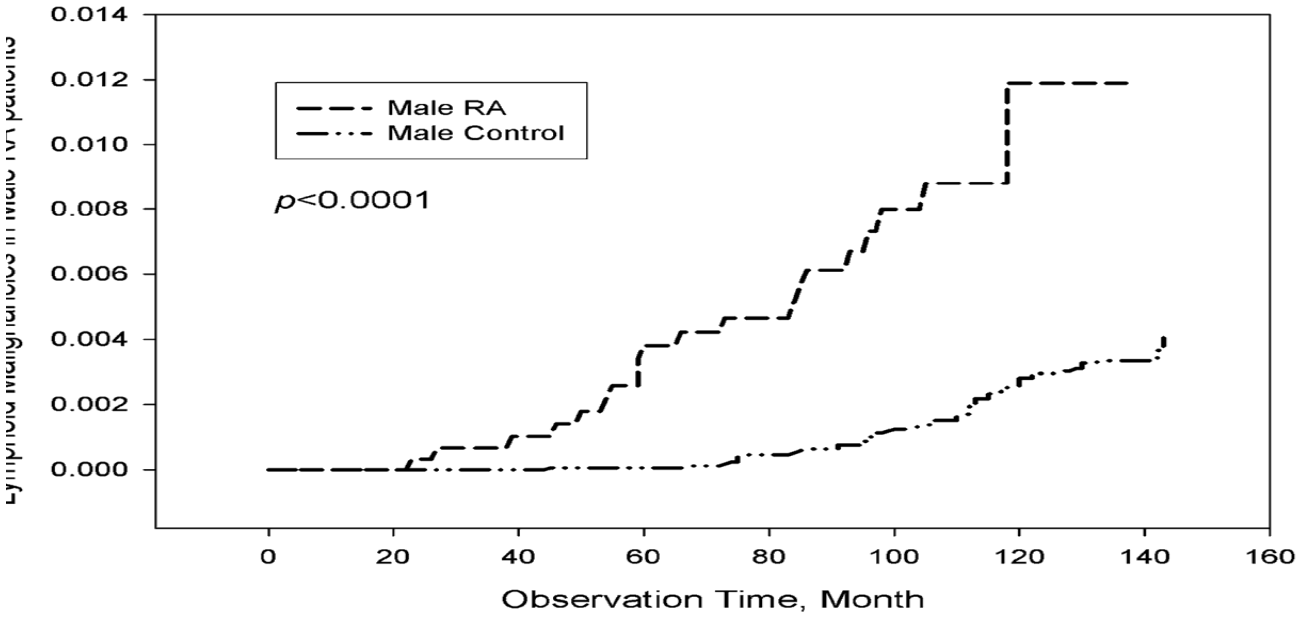
1997-2008 Taiwan National Health Insurance Database

No analysis upon disease activity or treatment protocols

Results

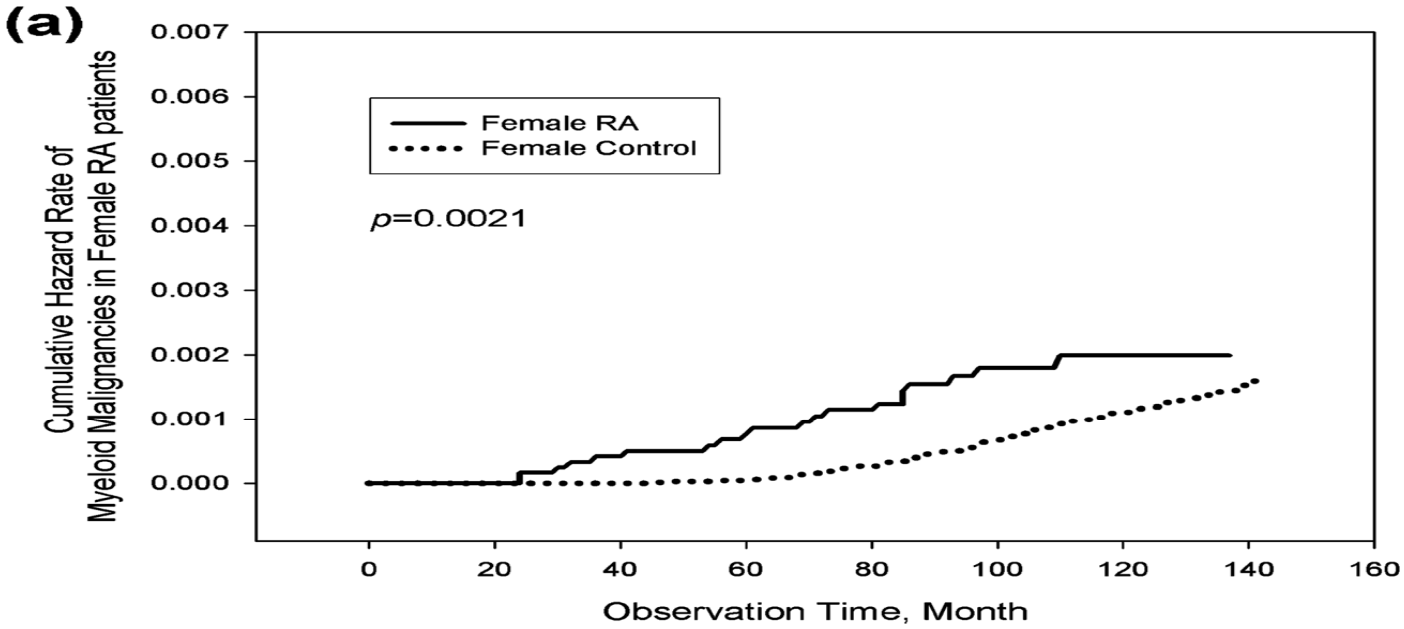
Lymphoid malignansies

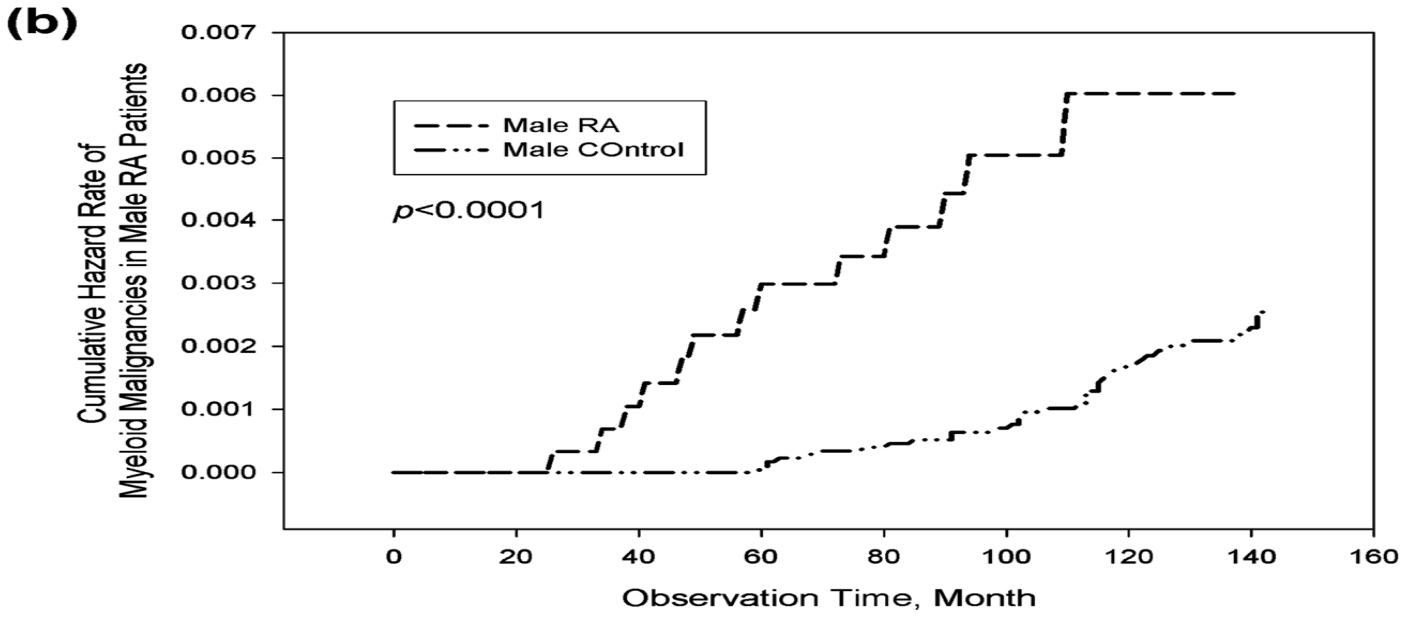




Results

Myeloid malignancies





Risk of solid cancer in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis

Mercer LK, et al Ann Rheum Dis 2015 Jun; 74(6): 1087-93

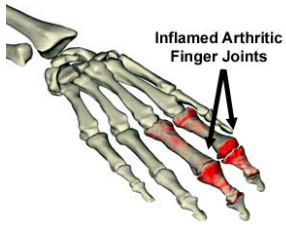
Objectives

To compare the risk of solid cancer in patients with RA treated with TNFi to that in patients treated sDMARDs

52549	11672
427 cancers	136 cancers

Conclusions

The addition of TNFi to sDMARD does not alter the risk of cancer in RA patients selected for TNFi in the UK.



ΕΥΧΑΡΙΣΤΩ