Porto's Autoimmune Meeting

25 - 27 Sept 2014
HF Ipanema Park

Classic DMARD's, biologic drugs and cancer risk

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Disclosure slide

I provided consultations or attended advisory boards for Astra-Zeneca, Eli Lilly Oncology, F. Hoffman-La Roche Ltd, Merck, Astellas and Pfizer, for which I received appropriate honoraria.

DMARD’s – Disease-Modifying Anti-Rheumatic Drugs

Patients with rheumatoid arthritis (RA) and other chronic inflammatory diseases are often subject to prolonged treatment with immunosuppressive drugs which modify the immunologic pathways involved in the pathogenesis of RA.

DMARD's – Disease-Modifying Anti-Rheumatic Drugs

Tumor necrosis factor alpha (TNFα) is among the cytokines that play a major role in the inflammatory process of rheumatic diseases.

Its inhibition leads to substantial improvement in clinical signs and symptoms in a majority of patients.

TNFα is able to induce tumor cell apoptosis led it to be named TNF before its role in the inflammatory process was revealed.

TNFα or rather its nuclear factor-kappa B pathway acts as an early tumor suppressor.

This property led to concerns about a possibly increased risk of malignancies when drugs blocking TNFα will be used for long-term treatment.

Anti-TNF antibody therapy in RA and risk of cancer

Meta-analysis

REVIEW

Anti-TNF Antibody Therapy in Rheumatoid Arthritis and the Risk of Serious Infections and Malignancies

Systematic Review and Meta-analysis of Rare Harmful Effects in Randomized Controlled Trials

Tim Bongartz, MD
Alex J. Sutton, PhD
Michael J. Sweeting, MSc
Iain Buchan, MD, MFPH
Eric L. Matteson, MD, MPH
Victor Montori, MD, MSc

Bongartz T, et al. JAMA 295:2275-2285, 2006

Anti-TNF antibody therapy in RA and risk of cancer

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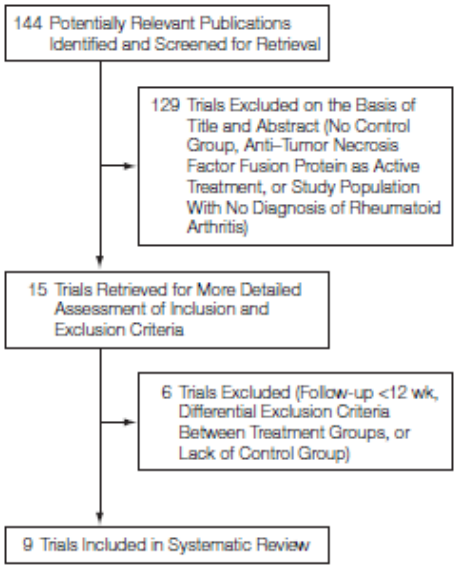
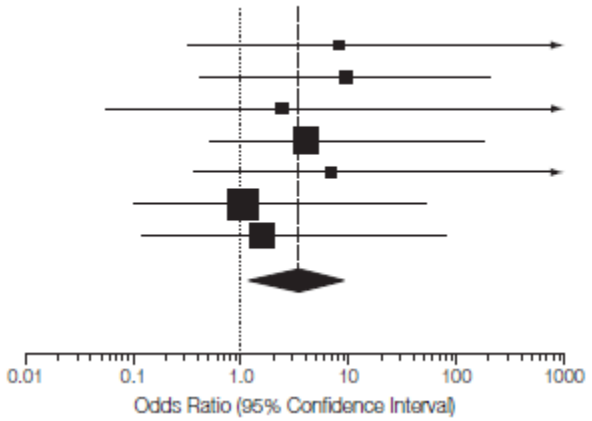


Source	Malignancies, No./Total		Odds Ratio (95% Confidence Interval)
	Anti-TNF	Placebo	
Lipsky et al,[9] 2000	5/342	0/86	7.57 (0.30-Infinity)
Furst et al,[8] 2003	4/318	0/318	9.11 (0.40-199.49)
Weinblatt et al,[11] 2003	1/209	0/62	2.29 (0.06-Infinity)
Keystone et al,[6] 2004	8/419	1/200	3.87 (0.51-172.73)
St Clair et al,[7] 2004	4/749	0/291	6.58 (0.36-Infinity)
Van de Putte et al,[33] 2004	4/434	1/110	1.01 (0.10-50.39)
Westhovens et al,[34] 2004	3/721	1/361	1.50 (0.12-79.18)
Total	29/3192	3/1428	3.29 (1.19-9.08)

Test for overall effect:
Mantel-Haenszel $\chi^2 = 5.2$; $P = .02$



Bongartz T, et al. JAMA 295:2275-2285, 2006

Anti-TNF antibody therapy in RA and risk of cancer

Meta-analysis

	Anti-TNF–Treated Participants (n = 3493)			Controls (n = 1512)	
Source	Type of Malignancy Among Patients With ≥1 Malignancy	Dosage	Time of Diagnosis, wk	Type of Malignancy Among Patients With ≥1 Malignancy	Time of Diagnosis, wk
Maini et al,[32] 1998	0			0	
Lipsky et al,[9] 2000	1 Lymphoma	Infliximab, 10 mg every 4 wk	26	0	
	1 Rectal carcinoma	Infliximab, 10 mg every 8 wk	26		
	1 Breast cancer	Infliximab, 10 mg every 4 wk	19		
	1 Malignant melanoma + squamous cell carcinoma	Infliximab, 10 mg every 4 wk	26		
		Infliximab, 10 mg every 8 wk	8		
	1 Basal cell carcinoma + recurrence				
Furst et al,[8] 2003	1 Basal cell carcinoma†	Adalimumab, 40 mg every other wk	3	0	
	1 Lymphoma (T cell)	Adalimumab, 40 mg every other wk	9		
	1 Basal cell carcinoma†	Adalimumab, 40 mg every other wk	10		
	1 Basal cell carcinoma†	Adalimumab, 40 mg every other wk	19		
	1 Lymphoma (large B cell)†‡	Adalimumab, 40 mg every other wk	38		
	1 Lymphoma (large B cell)†‡	Adalimumab, 40 mg every other wk	97		
Van de Putte et al,[10] 2003	0			0	
Weinblatt et al,[11] 2003	1 GI adenocarcinoma	Adalimumab, 80 mg every other wk	18	0	
Keystone et al,[6] 2004	1 Seminoma	Adalimumab, 20 mg weekly	8	1 Basal cell carcinoma	24
	1 Basal cell carcinoma†	Adalimumab, 20 mg weekly	8		
	1 GI adenocarcinoma	Adalimumab, 40 mg every other wk	14		
	1 Lymphoma (mixed B cell)	Adalimumab, 20 mg weekly	21		
	1 Basal cell carcinoma†	Adalimumab, 40 mg every other wk	22		
	1 Basal cell carcinoma†	Adalimumab, 40 mg every other wk	27		
	1 Squamous cell carcinoma†	Adalimumab, 40 mg every other wk	28		
	1 Breast cancer	Adalimumab, 40 mg every other wk	43		
	1 Lymphoma (B cell)†‡		67		
	1 Lymphoma (Hodgkin)†‡		88		
	1 Lymphoma (mixed B cell)†‡		114		
St Clair et al,[7] 2004	1 Leukemia	Infliximab, 6 mg every 4 wk	52	0	
	1 Endometrial cancer	Infliximab, 6 mg every 4 wk	3		
	1 Pancreatic cancer	Infliximab, 6 mg every 4 wk	15		
	1 GI adenocarcinoma	Infliximab, 6 mg every 4 wk	45		
Van de Putte et al,[33] 2004	1 Cholangiocarcinoma	Adalimumab, 40 mg every other wk	2	1 Basal cell carcinoma	6
	1 GI adenocarcinoma	Adalimumab, 40 mg weekly	9		
	1 Squamous cell carcinoma	Adalimumab, 40 mg every other wk	7		
	1 Basal cell carcinoma	Adalimumab, 20 mg every other wk	20		
	1 Lymphoma (mucosa-associated lymphoid tissue)†‡	NA	102		
Westhovens et al,[34] 2004	1 Lung cancer	Infliximab, 10 mg every 8 wk	6	1 Renal cell carcinoma	6
	1 Lung cancer	Infliximab, 10 mg every 8 wk	6		
	1 Lymphoma	Infliximab, 3 mg every 8 wk	7		

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Conclusions There is evidence of an increased risk of serious infections and a dose-dependent increased risk of malignancies in patients with rheumatoid arthritis treated with anti-TNF antibody therapy. The formal meta-analysis with pooled sparse adverse events data from randomized controlled trials serves as a tool to assess harmful drug effects.

Bongartz T, et al. JAMA 295:2275-2285, 2006

European countries biologics registers

European Biologics Registers	
Denmark	DANBIO
Germany	RABBIT
France	AIR ORA RATIO REGATE
Greece	HBR
Great Britain	BSRBR
Italy	GISEA MONITOR-NET
Netherlands	DREAM
Norway	NOR-DMARD
Sweden	ARTIS
Switzerland	SCQM
Spain	BIOBADASER
Czech Republic	ATTRA

German biologics register RABBIT

Strangfeld *et al. Arthritis Research & Therapy* 2010, **12**:R5
http://arthritis-research.com/content/12/1/R5

arthritis research&therapy

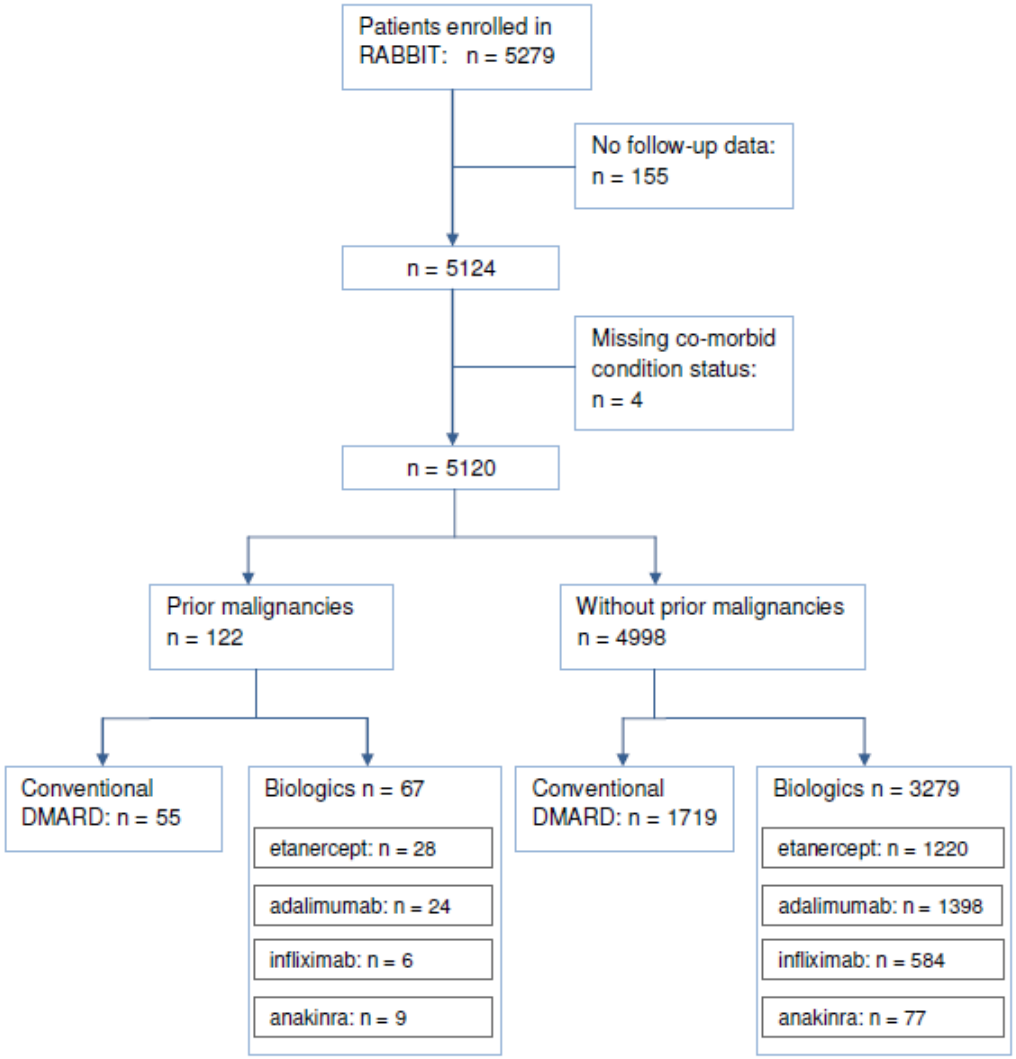
RESEARCH ARTICLE Open Access

Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT

Anja Strangfeld*[1], Franka Hierse[1], Rolf Rau[2], Gerd-Ruediger Burmester[3], Brigitte Krummel-Lorenz[4], Winfried Demary[5], Joachim Listing[1] and Angela Zink[1,3]

Strangfeld A, et al. Arthritis Res Ther 12:R5, 2010

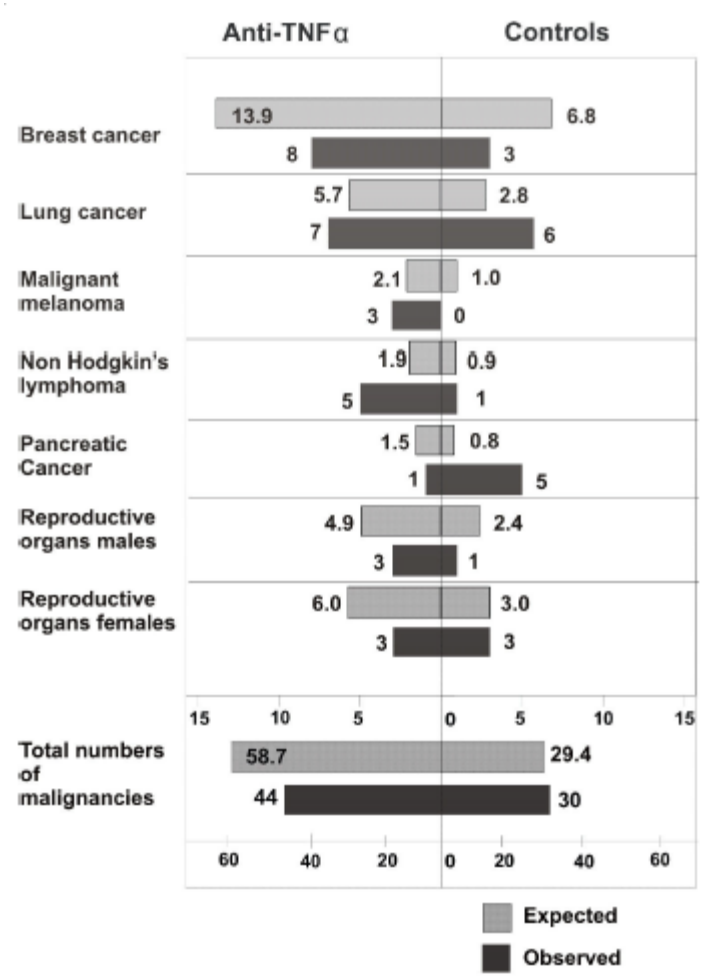
German biologics register RABBIT



Strangfeld A, et al. Arthritis Res Ther 12:R5, 2010

German biologics register RABBIT

Observed cancers and expected cancer from the general population, standardized by age and sex



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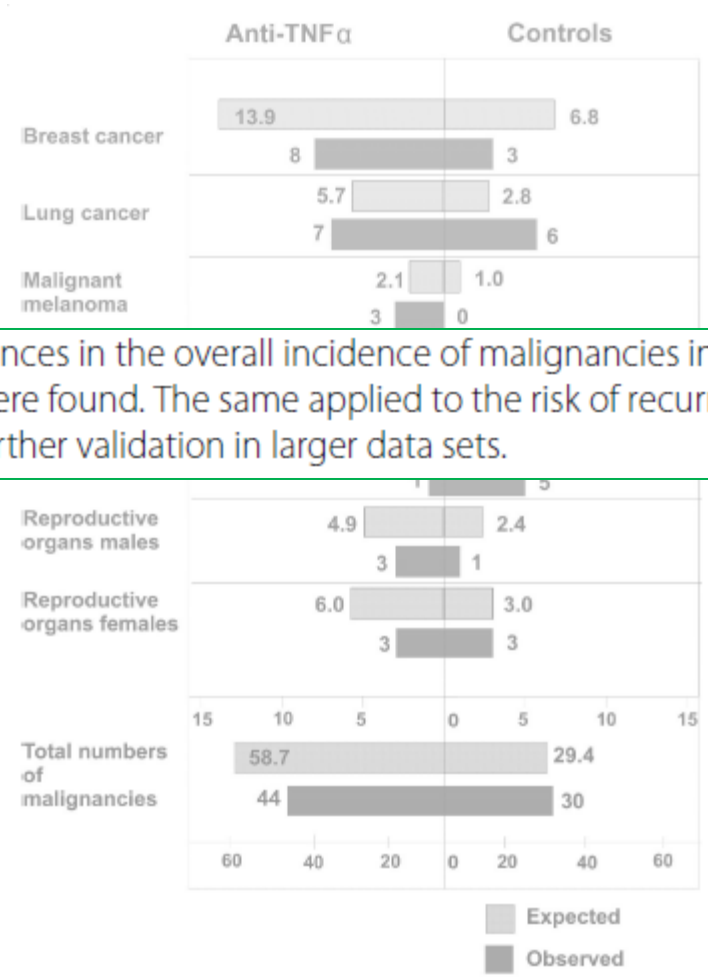


Conclusions: No significant differences in the overall incidence of malignancies in patients exposed or unexposed to anti-TNFα or anakinra treatment were found. The same applied to the risk of recurrent malignancies. However, in particular this last finding needs further validation in larger data sets.

Strangfeld A, et al. Arthritis Res Ther 12:R5, 2010

British Society for Rheumatology Biologics Register

Anti-TNF & cancer incidence in pts with AR and a prior malignancy

Arthritis Care & Research
Vol. 62, No. 6, June 2010, pp 755–763
DOI 10.1002/acr.20129

SPECIAL ARTICLE: DRUG SAFETY IN THE RHEUMATIC DISEASES

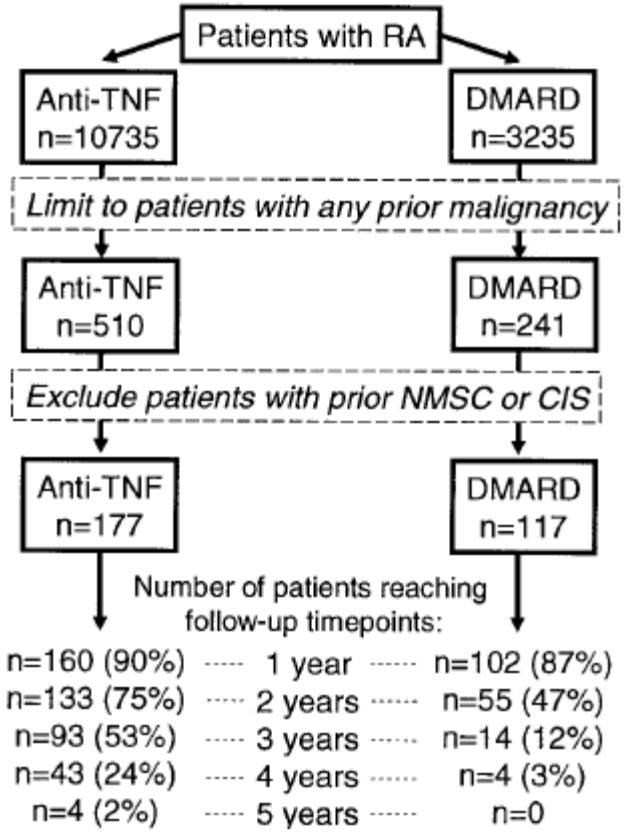
Influence of Anti–Tumor Necrosis Factor Therapy on Cancer Incidence in Patients With Rheumatoid Arthritis Who Have Had a Prior Malignancy: Results From the British Society for Rheumatology Biologics Register

W. G. DIXON, K. D. WATSON, M. LUNT, L. K. MERCER, BRITISH SOCIETY FOR RHEUMATOLOGY BIOLOGICS REGISTER CONTROL CENTRE CONSORTIUM, K. L. HYRICH, AND D. P. M. SYMMONS, ON BEHALF OF THE BRITISH SOCIETY FOR RHEUMATOLOGY BIOLOGICS REGISTER

Dixon WG, et al. Arthritis Care Res 62:755-763, 2010

British Society for Rheumatology Biologics Register

Anti-TNF & cancer incidence in pts with AR and a prior malignancy



NMSC – nonmelanoma skin cancer
CIS – carcinoma in situ

Dixon WG, et al. Arthritis Care Res 62:755-763, 2010

British Society for Rheumatology Biologics Register

Anti-TNF & cancer incidence in pts with AR and a prior malignancy

Baseline characteristics

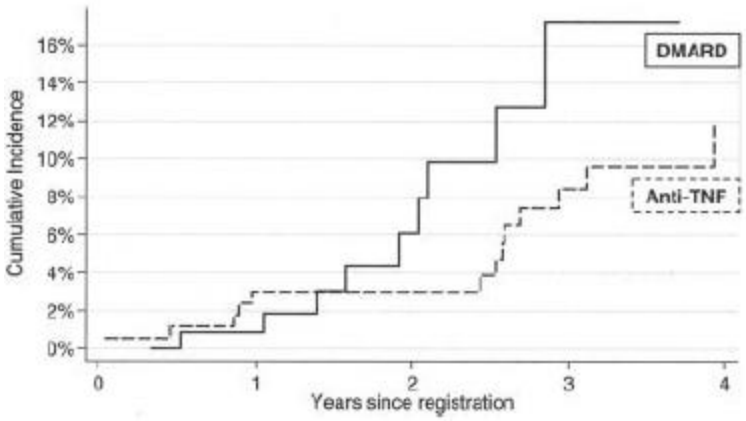
	DMARD (n = 117)	All anti-TNF (n = 177)	*P*
Age, mean ± SD years	66 ± 10	62 ± 10	0.002
Women, %	74	81	0.110
DAS28, mean ± SD	5.0 ± 1.3	6.7 ± 1.2	0.0001
HAQ score, mean ± SD	1.6 ± 0.7	2.2 ± 0.5	0.0001
Disease duration, median (IQR) years	9 (2–18)	11 (6–18)	0.0083
Prior DMARDs, median (IQR)	2 (1–4)	4 (3–5)	0.0001
Baseline steroid use	39 (33)	90 (51)	0.003
Smoking			
Current	25 (21)	32 (18)	0.011
Former	61 (52)	67 (38)	
Never	31 (27)	77 (44)	
Entry year			
Pre-2003	0	15 (8)	< 0.0001
2003	6 (5)	57 (32)	
2004	27 (23)	49 (28)	
2005	41 (35)	28 (16)	
2006 or after	43 (37)	28 (16)	
Prior malignancy			
Solid	96 (82)	147 (83)	0.795
Lymphoproliferative	11 (9)	13 (7)	
Melanoma	10 (8)	17 (10)	
Time from most recent prior malignancy to registration			
Median (IQR) years	8.5 (4.7–14.1)	11.5 (5.8–17.1)	0.027
>10 years preregistration	46 (39)	102 (58)	0.002

Dixon WG, et al. Arthritis Care Res 62:755-763, 2010

British Society for Rheumatology Biologics Register

Anti-TNF & cancer incidence in pts with AR and a prior malignancy

Cumulative incidence of malignancy and rate of incident cancers



	DMARD (n = 117)	All anti-TNF (n = 177)
Person-years of followup	232	503
Person-years followup per patient, median (IQR)	1.8 (1.3–2.6)	3.0 (1.9–3.9)
Incident malignancies, no.	9	11
Patients with incident malignancies, no.	9	11
Rate of incident malignancy/1,000 person-years (95% CI)	38.7 (17.7–73.5)	21.9 (10.9–39.2)
IRR (95% CI)	Referent	0.51 (0.2–1.27)
IRR adjusted for age and sex (95% CI)	Referent	0.52 (0.21–1.33)
Propensity-adjusted IRR (95% CI)	Referent	0.47 (0.10–2.22)

IRR – incidence rate ratio

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Anti-TNF & cancer incidence in pts with AR and a prior malignancy

Cumulative incidence of malignancy and rate of incident cancers

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IRR adjusted for age and sex (95% CI)	Referent	0.52 (0.21–1.33)
Propensity-adjusted IRR (95% CI)	Referent	0.47 (0.10–2.22)

Conclusion. **The way in which UK rheumatologists are selecting patients with RA and prior malignancy to receive anti-TNF therapy is not leading to an increased risk of incident malignancy. Although reassuring, these results should not be interpreted as indicating that it is safe to treat all RA patients with prior malignancy with anti-TNF therapy.**

Dixon WG, et al. Arthritis Care Res 62:755-763, 2010

British Society for Rheumatology Biologics Register

Etanercept & DMARD: long-term safety and survival

RHEUMATOLOGY

Rheumatology 2014;53:186–194
doi:10.1093/rheumatology/ket333
Advance Access publication 18 October 2013

Original article

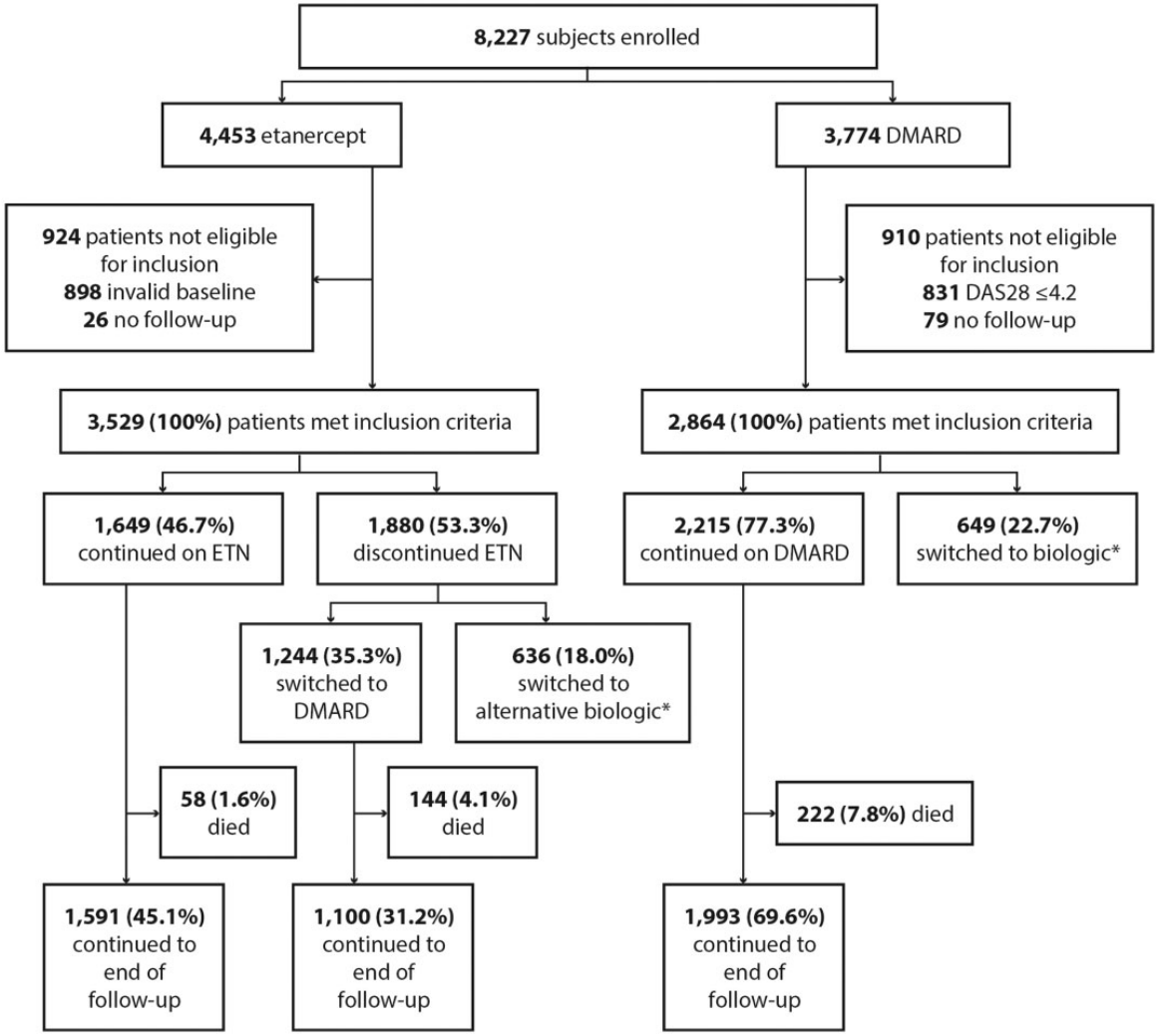
Treatment of rheumatoid arthritis with etanercept with reference to disease-modifying anti-rheumatic drugs: long-term safety and survival using prospective, observational data

Christopher Ll. Morgan[1], Paul Emery[2], Duncan Porter[3], Alan Reynolds[4], Adam Young[5], Helen Boyd[6], Chris D. Poole[1] and Craig J. Currie[1]

Morgan CL, et al. Rheumatology 53:186-194, 2014

British Society for Rheumatology Biologics Register

Etanercept & DMARD: long-term safety and survival



Morgan CL, et al. Rheumatology 53:186-194, 2014

British Society for Rheumatology Biologics Register

Etanercept & DMARD: long-term safety and survival

Parameter	Conventional DMARDs ($n = 2864$)	ETN ($n = 3529$)	*P*-value
Follow-up, person-years			
Total	11 095	16 919	
Mean (S.D.)	3.9 (2.0)	4.8 (2.4)	<0.001
Age, mean (S.D.), years	59.8 (12.4)	55.3 (12.1)	<0.001
Female sex, *n* (%)	2135 (74.5)	2727 (77.3)	0.011
Disease duration, mean (S.D.), years	9.6 (10.4)	13.5 (9.4)	<0.001
DAS28, mean (S.D.)	5.6 (0.9)	6.6 (1.0)	<0.001
HAQ, mean (S.D.)	1.6 (0.7)	2.1 (0.6)	<0.001
Patient has ever been RF positive, *n* (%)	2295 (65.0)	1665 (58.1)	<0.001
Patient has erosions on hand or foot X-rays, *n* (%)	2226 (63.1)	1309 (45.7)	<0.001
Previous DMARDs, mean (S.D.)	2.4 (1.6)	4.2 (1.8)	<0.001
ETN monotherapy, *n* (%)		1717 (48.7)	
Baseline DMARDs, mean (S.D.)	1.3 (0.6)	0.7 (0.8)	<0.001
Baseline other drugs, mean (S.D.)	4.4 (2.7)	4.4 (2.6)	0.59
Baseline steroids, *n* (%)	645 (22.5)	1710 (48.5)	<0.001
MTX, *n* (%)	1808 (63.1)	1175 (33.3)	<0.001
Prior steroids, *n* (%)	1601 (55.9)	2614 (74.1)	<0.001
Smoking history:			
Current smoker, *n* (%)	682 (23.8)	740 (21.0)	0.004
Ex-smoker, *n* (%)	1139 (39.8)	1380 (39.1)	
Non-smoker, *n* (%)	1029 (35.9)	1389 (39.4)	
Missing, *n* (%)	14 (0.5)	34 (1.0)	
BMI, mean (S.D.), kg/m^2	27.4 (6.8)	26.8 (6.0)	<0.001
Systolic blood pressure, mean (S.D.), mmHg	137.7 (20.5)	136.2 (20.4)	0.004
Diastolic blood pressure, mean (S.D.), mmHg	79.4 (11.2)	80.4 (11.0)	<0.001
Charlson co-morbidity index, mean (S.D.)	0.5 (0.9)	0.4 (0.8)	<0.001
Hypertension, *n* (%)	985 (34.4)	1151 (32.6)	0.536
Angina, *n* (%)	213 (7.4)	165 (4.7)	<0.001
Myocardial infarction, *n* (%)	128 (4.5)	114 (3.2)	0.006
Stroke, *n* (%)	100 (3.5)	70 (2.0)	<0.001
Epilepsy, *n* (%)	31 (1.1)	44 (1.2)	0.56
Asthma, *n* (%)	424 (14.8)	379 (10.7)	<0.001
Chronic obstructive pulmonary disease, *n* (%)	253 (8.8)	194 (5.5)	<0.001
Peptic ulcer disease, *n* (%)	191 (6.7)	323 (9.2)	<0.001
Liver disease, *n* (%)	58 (2.0)	102 (2.9)	0.016
Renal disease, *n* (%)	82 (2.9)	111 (3.1)	0.512
Tuberculosis, *n* (%)	62 (2.2)	94 (2.7)	0.199
Demyelination, *n* (%)	9 (0.3)	5 (0.1)	0.142
Diabetes, *n* (%)	203 (7.1)	218 (6.2)	0.144
Hyperthyroidism, *n* (%)	139 (4.9)	117 (3.3)	0.002
Depression, *n* (%)	490 (17.1)	701 (19.9)	0.007
Prior cancer, *n* (%)	205 (7.2)	125 (3.5)	<0.001

Morgan CL, et al. Rheumatology 53:186-194, 2014

British Society for Rheumatology Biologics Register

Etanercept & DMARD: long-term safety and survival

Adverse event category	Conventional DMARDs		ETN			
			All events		Exposure +90 days	
	n	Rate[a]	*n*	Rate[a]	*N*	Rate[a]
All-cause mortality	223	20.1	203	12.0	98	5.8
Serious infections	375	36.2	538	35.1	489	38.1
Pneumonia	225	21.1	205	12.5	179	13.3
Septicaemia	28	2.5	34	2.0	15	1.1
Bone/joint infection	31	2.8	83	5.0	72	5.3
Other serious infection	171	15.9	314	19.7	287	21.9
Cancer	254	23.9	241	14.7	185	13.8
Lymphoproliferative malignancies	29	2.6	18	1.1	13	0.9
Lymphoma	18	1.6	11	0.7	10	0.7
Myeloma	4	0.4	1	0.1	0	0.0
Leukaemia	7	0.6	6	0.4	3	0.2
Non-melanoma skin cancer	79	7.3	79	4.7	65	4.8
Solid tumours	158	14.6	153	9.2	112	8.2
Other serious adverse events	310	29.6	327	20.3	277	21.0
Cardiac events	192	17.9	165	10.0	136	10.1
Congestive heart failure	36	3.3	28	1.7	19	1.4
Myocardial infarction	69	6.3	65	3.9	53	3.9
Other cardiac events	102	9.4	85	5.1	72	5.3
CNS	97	8.9	127	7.7	109	8.1
Central demyelination	1	0.1	1	0.1	1	0.1
Optic neuritis	0	0.0	2	0.1	2	0.1
Peripheral neuropathy	12	1.1	10	0.6	6	0.4
Other CNS events	85	7.8	117	7.0	102	7.6
Haematological	59	5.4	57	3.4	51	3.7
Aplastic anaemia	0	0.0	1	0.1	1	0.1
Pancytopaenia	8	0.7	4	0.2	4	0.3
Agranulocytosis	0	0.0	2	0.1	1	0.1
Other dyscrasia	53	4.8	51	3.0	46	3.4
Leucopoenia	2	0.2	7	0.4	6	0.4
Pulmonary fibrosis	13	1.2	14	0.8	7	0.5

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Serious infections	375	36.2	538	35.1	489	38.1
Pneumonia	225	21.1	205	12.5	179	13.3
Septicaemia	28	2.5	34	2.0	15	1.1
Bone/joint infection	31	2.8	83	5.0	72	5.3
Other serious infection	171	15.4	314	19.7	187	21.9
Cancer	254	23.9	241	14.7	185	13.8
Lymphoproliferative malignancies	29	2.6	18	1.1	13	0.9
Lymphoma	18	1.6	11	0.7	10	0.7
Myeloma	4	0.4	1	0.1	0	0.0
Leukaemia	7	0.6	6	0.4	3	0.2
Non-melanoma skin cancer	79	7.3	79	4.7	65	4.8
Solid tumours	158	14.6	153	9.2	112	8.2
Cardiac events	192	17.8	165	10.0	136	10.1
Congestive heart failure	36	3.3	28	1.7	19	1.4
Myocardial infarction	69	6.3	65	3.9	53	3.9
Other cardiac events	102	9.4	85	5.1	72	5.3
CNS	97	8.9	127	7.7	109	8.1
Central demyelination	1	0.1	1	0.1	1	0.1
Optic neuritis	0	0.0	2	0.1	2	0.1
Peripheral neuropathy	12	1.1	10	0.6	6	0.4
Other CNS events	85	7.8	117	7.0	102	7.6
Haematological	59	5.4	57	3.4	51	3.7
Aplastic anaemia	0	0.0	1	0.1	1	0.1
Pancytopaenia	8	0.7	4	0.2	4	0.3
Agranulocytosis	0	0.0	2	0.1	1	0.1
Other dyscrasia	53	4.8	51	3.0	46	3.4
Leucopoenia	2	0.2	7	0.4	6	0.4
Pulmonary fibrosis	13	1.2	14	0.8	7	0.5

Morgan CL, et al. Rheumatology 53:186-194, 2014

British Society for Rheumatology Biologics Register

Etanercept & DMARD: long-term safety and survival

Pts with prior cancer aHR=0.877 (95% CI 0.720, 1.069, *P* = 0.194)

Pts without prior cancer aHR=0.804 (95% CI 0.460, 1.403, *P* = 0.442)

Safety parameters	All events				Exposure + 90 days			
	aHR	95% CI		*P*-value	aHR	95% CI		*P*-value
All-cause mortality	0.717[a]	0.537	0.958	0.024	0.435[g]	0.314	0.604	<0.001
Serious infections	1.019[b]	0.831	1.251	0.855	1.072[h]	0.879	1.307	0.493
Cancer	0.836[c]	0.683	1.025	0.084	0.834[i]	0.682	1.018	0.075
Lymphoproliferative malignancies	0.512[d]	0.276	0.952	0.035	0.458[j]	0.229	0.918	0.028
Other serious adverse events	0.700[e]	0.564	0.870	0.001	0.850[k]	0.664	1.087	0.195
Cardiac events	0.518[f]	0.374	0.719	<0.001	0.563[l]	0.402	0.788	0.001

Morgan CL, et al. Rheumatology 53:186-194, 2014

EULAR recommendations for management of RA

Safety of synthetic and biological DMARDs

Clinical and epidemiological research

EXTENDED REPORT

Safety of synthetic and biological DMARDs: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis

Sofia Ramiro,[1,2] Cécile Gaujoux-Viala,[3] Jackie L Nam,[4,5] Josef S Smolen,[6,7] Maya Buch,[4,5] Laure Gossec,[8] Désirée van der Heijde,[9] Kevin Winthrop,[10] Robert Landewé[1,11]

Ramiro S, et al. Ann Rheum Dis 73:529-535, 2014

EULAR recommendations for management of RA

Safety of synthetic and biological DMARDs

ABSTRACT

Objectives To update the evidence for the safety of synthetic disease-modifying antirheumatic drugs (sDMARDs), glucocorticoids (GC) and biological DMARDs (bDMARDs) in patients with rheumatoid arthritis (RA) to inform the European League Against Rheumatism (EULAR) recommendations for the management of RA.

Methods Systematic literature review (SLR) of observational studies (including registries). Interventions were any bDMARD (anakinra, infliximab, etanercept, adalimumab, rituximab, abatacept, tocilizumab, golimumab or certolizumab pegol) or sDMARD (methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, gold/auranofin, azathioprine, chlorambucil, chloroquine, cyclosporin, cyclophosphamide, mycophenolate, minocycline, penicillamine, tacrolimus or tofacitinib) and a comparator was required. Information on GCs was collected from the included studies. All safety outcomes were included.

Results Forty-nine observational studies addressing diverse safety outcomes of therapy with bDMARDs met eligibility criteria. Substantial heterogeneity precluded meta-analysis of any of the outcomes. Patients on tumour necrosis factor inhibitors (TNFi) compared to patients on conventional sDMARDs had a higher risk of serious infections (adjusted HR (aHR) 1.1–1.8), a higher risk of tuberculosis, and an increased risk of infection by herpes zoster cannot be excluded. Patients on TNFi did not have an increased risk for malignancies in general, lymphoma or non-melanoma skin cancer, but the risk of melanoma may be slightly increased (aHR 1.5). From the studies identified on conventional sDMARDs, no new safety signals were found.

Conclusions The findings from this SLR confirm the known safety pattern of sDMARDs and bDMARDs for the treatment of RA.

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Study ID	Registry	Intervention	Control csDMARDs	Control general population	aHR (Intervention vs comparator/control)	aHR (intervention vs general population)	Risk of bias
All types of cancer							
Askling (2009) *A&R*[33]	ARTIS	3 TNFi	csDMARDs	General population	TNFi vs pts starting MTX: 1.0 (0.8, 1.2); TNFi vs csDMARDs combination therapy 1.0 (0.7, 1.4)	1.1 (1.0, 1.3)	Low
Carmona (2011) *Semin Arthritis Rheum*[34]	BIOBADASER	3 TNFi	csDMARDs	General population	0.5 (0.1, 2.5)	0.7 (0.5, 0.9)	Low
Hayes (2013) *A&R*[35]	Claim database	3 TNFi	csDMARDs	NA	0.8 (0.6, 1.1); ever-analysis 0.9 (0.8, 1.1)	NA	Moderate
Pallavicini (2010) *Autoimmunity Reviews*[36]	LORHEN	3 TNFi	NA	General population	NA	Milan*: 0.9 (0.6, 1.5), Varese 1.1 (0.6, 1.7); Solid cancer Milan: 0.7 (0.4, 1.2), Varese 0.9 (0. 5, 1.5)	Moderate
Strangfeld (2010) *AR&T*[37]	RABBIT	3 TNFi +anakinra	csDMARDs	General population	TNFi vs csDMARDs 0.7 (0.4, 1.1); ANA vs csDMARDs 1.4 (0.6, 3.5)	0.8 (0.5, 1.0)	Low
Patients with history of cancer							
Dixon (2010) *AC&R*[38]	BSRBR	3 TNFi	csDMARDs	NA	0.5 (0.1, 2.2); Censoring after 1st cancer 0.5 (0.1, 2.2)	NA	Low

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Study ID	Registry	Intervention	Control csDMARDs	Control general population	aHR (Intervention vs comparator/control)	aHR (intervention vs general population)	Risk of bias
Lymphoma							
Askling (2009) *ARD*[39]	ARTIS	3 TNFi	csDMARDs	General population	1.4 (0.8, 2.1)	2.7 (1.8, 4.1)	Low
Mariette (2010) *ARD*[40]	RATIO	3 TNFi		General population	NA	2.3 (1.6, 3.3)	Low
Carmona (2011) *Semin Arthritis Rheum*[34]	BIOBADASER	3 TNFi	csDMARDs	General population	NA	Hodgkin 5.3 (0.1, 29.5); non-Hodgkin 1.5 (0.31, 4.4)	Low
Haynes (2013) *A&R*[35]	Claim database	3 TNFi	csDMARDs	NA	0.8 (0.3, 2.1), ever-analysis 1.3 (0.7, 2.2); any lymphoma or leukemia: 0.7 (0.3, 1.5); ever-analysis (1.0 (0.6, 1.6)	NA	Moderate
Pallavicini (2010) *Autoimmunity Reviews*[36]	LOHREN	3 TNFi	NA	General population	NA	Milan 6.0 (1.6, 15.4), Varese 5.0 (1.3, 12.7); Haematological cancer Milan 4.1 (1.3, 9.5), Varese 4.1 (1.3, 9.5)	Moderate
Non-melanoma skin cancer							
Amari (2011) *Rheumatology*[41]	Claim database	3 TNFi	csDMARDs	NA	1.4 (1.2, 1.6); TNFi vs MTX 1.4 (1.2, 1.7)	NA	Moderate
Mercer (2012) *ARD*[42]	BSRBR	3 TNFi	csDMARDs	General population	BCC 1.0 (0.5, 1.7), SCC 1.2 (0.4, 3.8); 1st cancer per subject BCC 0.8 (0. 5, 1.5)	1.7 (1.4, 2.0)	Low
Haynes (2013) *A&R*[35]	Claim database	3 TNFi	csDMARDs	NA	0.8 (0.5, 1.4); ever-analysis 1.1 (0.8, 1.5)	NA	Moderate
Melanoma							
Raaschou (2013) *BMJ*[43]	ARTIS	5 TNFi	csDMARDs	NA	1.5 (1.0, 2.2)	NA	Low

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Study ID	Registry	Intervention	Control csDMARDs	Control general population	aHR (Intervention vs comparator/control)	aHR (intervention vs general population)	Risk of bias
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Askling (2009) *ARD*[39]	ARTIS	3 TNFi	csDMARDs	General population	1.4 (0.8, 2.1)	2.7 (1.8, 4.1)	Low
Mariette (2010) *ARD*[40]	RATIO	3 TNFi		General population	NA	2.3 (1.6, 3.3)	Low
Carmona (2011) *Semin Arthritis Rheum*[34]	BIOBADASER	3 TNFi	csDMARDs	General	NA	Hodgkin 5.3 (0.1, 29.5); n 1.5 (0.31, 4.4)	Low
Haynes (2013) *A&R*[35]							Moderate
Pallavicini (2010) *Autoimmu Reviews*[36]				population		l.6, 15.4), Varese 5.0 (1.3, 12.7); Haematological cancer Milan 4.1 (1.3, 9.5), Varese 4.1 (1.3, 9.5)	Moderate
Non-melanoma skin cancer							
Amari (2011) *Rheumatology*[41]	Claim database	3 TNFi	csDMARDs	NA	1.4 (1.2, 1.6); TNFi vs MTX 1.4 (1.2, 1.7)	NA	Moderate
Mercer (2012) *ARD*[42]	BSRBR	3 TNFi	csDMARDs	General population	BCC 1.0 (0.5, 1.7), SCC 1.2 (0.4, 3.8); 1st cancer per subject BCC 0.8 (0. 5, 1.5)	1.7 (1.4, 2.0)	Low
Haynes (2013) *A&R*[35]	Claim database	3 TNFi	csDMARDs	NA	0.8 (0.5, 1.4); ever-analysis 1.1 (0.8, 1.5)	NA	Moderate
Melanoma							
Raaschou (2013) *BMJ*[43]	ARTIS	5 TNFi	csDMARDs	NA	1.5 (1.0, 2.2)	NA	Low

Conclusions The findings from this SLR confirm the known safety pattern of sDMARDs and bDMARDs for the treatment of RA.

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Conclusions

1. Many randomised controlled trials have been undertaken providing data on the short-term safety of disease-modifying antirheumatic drugs (DMARDs).

2. A milestone in the management of RA has been the development of registries for the long-term evaluation of the safety and effectiveness of both sDMARDs and bDMARDs.

    - Registries following large cohorts of real-world RA patients provide estimates of risk for several agents.

3. The findings from clinial trials and published literature confirm the safety pattern of sDMARDs and bDMARDs for the treatment of RA.

4. Overall, the safety of biologic and non-biologic DMARDs appears to be reasonable, particularly compared with the risks associated with the disease itself.

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