Adverse events and infections in patients with rheumatoid arthritis treated with conventional drugs or biologic agents: a real world study

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Abstract

Objective

Treatment of rheumatoid arthritis (RA) with disease-modifying anti-rheumatic drugs (DMARDs), either synthetic (sDMARDs) or biologic agents (bDMARDs) has significantly improved disease outcome. However, the impact of therapy-related adverse events (AEs), mild, moderate or serious, on disease outcome is under debate. The purpose of the study was to test the hypothesis that AEs, including infections, are rather common in patients receiving bDMARDs than in those receiving sDMARDs.

Methods

Analysis of the medical records of patients followed in a single outpatient clinic was performed. In total, 1403 adults (295 men, 1108 women) were included in the analysis (969 treated with sDMARDs only, 434 with bDMARDs). All AEs and infections were recorded and their severity was graded according to international criteria. Incident rates were calculated and Kaplan-Meier plots as well as Cox proportional-hazards models were performed to examine the association of treatment groups with the risk of any AE.

Results

The risk of any AE, irrespective of severity, was significantly higher in patients with bDMARDs with the adjusted hazard ratio being 1.98 (95% CI: 1.64 to 2.39). Patients in the biologic group treated initially with infliximab or adalimumab had a higher risk of AE compared to patients receiving etanercept or other biologic agents. Among patients treated with methotrexate, those receiving a dose below 10 mg had a higher risk of any AE when compared to those receiving higher doses.

Conclusion

The risk of any AE among RA patients treated with bDMARDs was significantly higher compared to those treated with sDMARDs.

Key words

rheumatoid arthritis, adverse events, infections, biologic agents, disease-modifying anti-rheumatic drugs

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Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory disease of small and large joints resulting in their destruction and functional impairment, with permanent disability and reduced survival of patients, due to therapy or disease related co-morbidities (1).

Intensive treatment with disease-modifying anti-rheumatic drugs (DMARDs), either synthetic (sDMARDs) or biologic (bDMARDs), has dramatically reduced disability in these patients (2-4). Mortality rates of RA have been gradually improved over the last decades but still remain higher than in the general population, raising questions on treatment safety and long-term efficacy (5, 6). The short duration of use of bDMARDs is not probably enough to give prominence to decreased mortality; alternatively these agents may not be superior to sDMARDs in long-term. Recent reports underline the increased risk for infections in patients taking anti-tumour necrosis factor α (anti-TNF-α) monoclonal antibodies or other bDMARDs, while other attribute the infections to the co-administration of corticosteroids (7, 8). On the contrary, it was recently shown that anti-TNF-α agents and rituximab decrease mortality by reducing disease activity (9). The short duration of registration trials regarding biologic treatments, absence of co-morbidities, younger average age and discontinuation of observation after treatment failure or after the presence of any adverse event (AE), probably explain the relative absence of severe AEs in the initial reports.

Study objectives were to test the hypothesis that the risk for treatment-related AE (including any AE or infection), was more common among RA-patients treated with bDMARDs than those treated with sDMARDs and to compare the risk of any first AE across specific biologic agents.

Materials and methods

Study population

The files of patients with RA, according to international classification criteria, followed between 1985 and 2013 in the Rheumatology Department in "Laiko" University Hospital of Athens' Medical School, were retrospectively evaluated. Each visit was separately recorded for all patients. Initially the files of 1663 RA patients with detailed information on several variables were selected. After excluding those younger than 18 years, those followed-up less than 3 months or those receiving only steroids, 1403 adults (295 men and 1108 women) were included. All patients were evaluated for latent or active tuberculosis according to international guidelines and treated appropriately (10). The study protocol was approved by the Ethics Committee of the university hospital and was consistent with the principles of the declaration of Helsinki.

Study outcomes

Severity of AEs was classified according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4.03, 2010, U.S. Department of Health and Human Services), which is a 5 grade severity system as follows: 1=mild (asymptomatic or mild symptoms, clinical or diagnostic observation only, intervention not indicated), 2=moderate (minimal, local or non-invasive intervention indicated), 3=severe but not immediately life-threatening (hospitalisation indicated), 4=life-threatening consequences (urgent intervention indicated), 5=death. Grades 1 and 2 are considered as mild, not necessitating admission in hospital, while grades 3–5 are considered as serious. The primary outcome studied was the first AE, irrespective of severity, encountered during follow-up within the hospital. Secondary outcomes were the first serious AE, the first infection and the first serious infection occurred. If a patient had multiple outcomes during follow-up, he/she was counted only once in the survival analysis.

Treatment groups

Patients with RA who had been treated with any bDMARD (since 1997, after biologic treatment was approved in Greece for prospective trials or for routine care later on), irrespective of any previous or parallel treatment with sDMARDs, comprised the "biologic" group. In total 434 individuals had received one or more bDMARDs, among

whom 40% switched to second biologics. Patients were further separated into 4 categories according to the specific bDMARD they initially received at the hospital: infliximab, adalimumab, etanercept or any other biologic agent.). The remaining 969 patients treated only with sDMARDs comprised the comparison group ("DMARDS only") and 71% of them (691 cases) had received only methotrexate (MTX). The rest of patients in the "DMARDS only" group had received either leflunomide (5%) or other sDMARD (15%) or a combination of sDMARDs (9%) including MTX for some of them, unless contraindicated.

Assessment of covariates

Baseline information was collected for all patients with regard to demographic and disease related data, while for the latter, many of the related variables were recorded at every visit. Among the several variables collected were: sex, age at initiation of follow-up (when receiving the first anti-rheumatic treatment), type, duration, dose and sequence of administration of each drug following the first one, as well as erythrocyte sedimentation rate (ESR) in 2 categories (<40 and ≥40 mm/hour), initial and final disease activity according to Disease Activity Score (DAS-28, 3 variables) in 4 categories (>5.1, 3.2–5.1, 2.6–3.2 and ≤2.6), tender and swollen joint count, (<5, 6–10 and ≥11), type of joints (small, large or both), extra-articular manifestations (no, yes), titers of rheumatoid factor (RF) in 4 categories (≤49, 50–99, 100–199 and ≥200 units/mL) including an extra category of missing/unknown information, smoking status (never, former, current) and co-morbidities at first treatment initiation [cardiovascular disease (CVD), cancer, metabolic disease (diabetes mellitus, dyslipidaemia, obesity), lung disease, gastrointestinal and liver disease, tuberculosis, viral hepatitis, neuropsychiatric disease, renal or thyroid disease]. Mean and cumulative (total) dose of steroids were additionally calculated. Tempo of administration of each treatment was also subdivided into 3 categories and recorded as: very early, early and late (≤3, 4–12 and ≥13 months respectively after the first disease-related symptoms).

Statistical analysis

For descriptive purposes, study characteristics are presented either as mean and standard deviation for continuous variables or as frequencies and percentages for categorical variables, by treatment group and by specific bDMARD. T-tests (or Kruskal-Wallis non-parametric test for the specific bDMARDs) and Chi-square tests were applied, respectively.

Incident rates (IR) of AEs, presented as events/100 person-years (PY), and the corresponding incident rate ratios (IRRs) were calculated based initially on all reported events occurred during follow-up: individuals in the biologic group contributed PY from the initiation of their biologic treatment up until the end of the period in which they were treated with one or more bDMARDs. The duration of follow-up preceding the initiation of bDMARD, during which they received any sDMARD(s), was included in the comparison group. Patients in the "DMARDs only" group, contributed PY from the time of initiation of sDMARD treatment till last follow-up time checked. Subsequently, rates of the first AE or serious AE (CTCAE score 3–5) and the first infection or serious infection, as well as the corresponding IRRs, were estimated based on the PY contributed by patients, only for the period from the initiation of the bDMARD, or the first sDMARD, up until the time which the first AE or infection occurred.

Kaplan-Meier (KM) plots with logrank tests were applied and subsequent multivariate Cox proportional-hazards analyses were performed in order to assess the association of the treatment group (or the specific bDMARD) with the risk of first AE (irrespective of severity of AE or infection), after adjusting for several potential confounders. In all models length of follow-up (in months) until the first AE was the primary time variable and patients without AEs were censored at the end of the period of follow-up receiving sDMARDs only (comparison group) or bDMARDs (biologic group). If an AE occurred after the patient had discontinued a biologic agent, that event was not included in the analysis. We included as confounders in the multivariate models those that were found to be significantly associated with the primary outcome (any AE occurred first) or to substantially alter the absolute change of the effect estimate of the main exposure variable (treatment group) after applying the relevant bivariate Cox models. The proportional hazards assumption was evaluated through the use of time-varying covariates. The multivariate analyses using the extracted confounders were repeated for the secondary outcomes.

Sensitivity analyses were run after excluding those patients with less than 6 months of follow-up. Moreover, a) specific bDMARDs were compared and b) for patients being treated only with MTX the potential association of mean MTX dose with the risk of AE was examined. Data were analysed using STATA (Stata/SE 11.0. for Windows; Stata Corporation, College Station, TX, USA).

Results

Patient characteristics

Study-sample characteristics for the 1403 patients with RA are presented in Table I. A higher percentage of both tender and swollen joints, extra-articular manifestations, total steroid dose ≥500 mg and ESR ≥40 mm/hour were found in the biologic group, whose patients were on average younger than those in the comparison group (p=0.014, Table I).

Incident rates and ratios

There were 519 AEs in the biologic group with an IR of 35.5 events/100 PY, corresponding to an IRR of 2.24 (95% CI: 1.96–2.55), as compared with the respective 407 AEs and 15.9 events/100 PY in the "DMARDs only" group (Table II). When the duration of follow-up preceding the initiation of biologic agent, during which the patients of the biologic group received sDMARDs, was incorporated in the "DMARDs only" group, the corresponding number of AEs for this group increased to 609 but the IR remained substantially lower compared to the

Table I. Frequency of adverse events and general characteristics in patients with rheumatoid arthritis by treatment group and specific bDMARD.

	sDMARDs only		All bDMARDs			Specific bDMARD taken first								
Number = 1403	969		434			Infliximab 129		Adalimumab 103		Etanercept 135		Other 67		
	n	%	n	%	*p**	n	%	n	%	n	%	n	%	*p**
Women	771	80	337	78	0.436	106	82	73	71	103	76	55	82	0.161
Incident case	509	53	164	38	<0.001	50	39	35	34	57	42	22	33	0.473
Early treatment (in months)					0.187									0.205
≤3	344	35	143	33		31	24	35	34	54	40	23	34	
4 to 12	329	34	137	32		43	33	33	32	39	29	22	33	
13+	296	31	154	35		55	43	35	34	42	31	22	33	
Tender joints					<0.001									<0.001
≤5	385	40	133	31		18	14	31	30	56	41	28	42	
6 to 10	257	27	100	23		28	22	22	21	36	27	14	21	
11+	327	34	201	46		83	64	50	49	43	32 (7)	25 (5)	37 (7)	
Type of joints					0.001									0.001
small	186	19	53	12		4	3	14	14	19	14	16	24	
large	161	17	60	14		13	10	12	12	27	20	8	12	
both	622	64	321	74		112	87	77	75	89	66	43	64	
Extra-articular manifestations	570	59	281	65	0.039	96	74	69	67	75	56	41	61	0.012
ESR (in mm/hour) 40+ †	521	55	291	68	<0.001	101	79	67	66	81	61	42	64	0.012
RF group (U/mL)					0.001									0.012
0 to 49	434	45	173	40		52	40	39	38	61	45	21	31	
50 to 99	81	8	42	10		12	9	8	8	15	11	7	10	
100 to 199	83	9	41	9		15	12	5	5	9	7	12	18	
200+	122	13	89	21		31	24	23	22	17	13	18	27	
missing/unknown	249	26	89	21		19	15	28	27	33	24	9	13	
Smoking status					0.916									0.001
Never	732	76	332	77		85	66	74	72	118	87	55	82	
Former	31	3	14	3		5	4	2	2	5	4	2	3	
Current	206	21	88	20		39	30	27	26	12	9	10	15	
Co-morbidities					0.254									0.804
No	470	48	220	51		66	51	51	50	70	52	33	49	
Yes	413	43	167	38		46	36	39	38	55	41	27	40	
missing/unknown	86	9	47	11		17	13	13	13	10	7	7	10	
Initial DAS-28					0.174									0.005
>5.2	417	43	196	45		73	57	48	47	50	37	25	37	
3.1 to 5.2	438	45	180	41		49	38	43	42	59	44	29	43	
2.6 to 3.1	59	6	22	5		2	2	6	6	7	5	7	10	
≤2.6	55	6	36	8		5	4	6	6	19	14	6	9	
Mean dose of steroids (mg/day)					0.004									<0.001
None	219	23	71	16		10	8	10	10	39	29	12	18	
<5	163	17	102	24		30	23	35	34	28	21	9	13	
5 to <10	510	53	231	53		81	63	52	50	59	44	39	58	
10+	77	8	30	7		8	6	6	6	9	7	7	10	
Total dose of steroids (mg)					<0.001									<0.001
<500	719	74	293	68		83	64	73	71	87	64	50	75	
≥500	31	3	70	16		36	28	20	19	9	7	5	7	
None	219	23	71	16		10	8	10	10	39	29	12	18	
	mean	SD	mean	SD		mean	SD	mean	SD	mean	SD	mean	SD	
Age (in yrs)	55.1	14.8	53.0	14.1	0.014	51.6	12.9	52.7	14.9	51.6	14.9	58.9	12.2	0.002
Initial DAS-28	4.9	1.3	4.9	1.5	0.655	5.3	1.3	5.0	1.5	4.6	1.6	4.6	1.4	<0.001
Tender joints	9	7.2	11	8.0	<0.001	14	7.4	11	8.5	9	7.7	8	6.8	<0.001
Swollen joints	5	4.3	5	3.9	<0.001	7	3.9	6	4.6	5	4.3	5	3.9	<0.001

**p*-value from Chi square test for categorical variables, from t-test for continuous (sDMARDs *vs*. bDMARDs) and Kruskal-Wallis test for continuous variable in case of specific bDMARDs. †21 cases with unknown/missing information.

Table II. Rates of adverse events (AEs) by treatment group.

	sDMARDs only	bDMARDs
Number	969	434
Including all adverse events and infections (some patients with >1)		
PY overall	2561 (3241*)	1460
No. of AE overall	407 (609*)	519
IR	15.89 (18.79*)	35.55
IRR (95% CI)	ref	2.24 (1.96 to 2.55)
	ref*	1.89 (1.68 to 2.13)
Including only first observed adverse event or infection		
PY for first AE	1809	750
No. of AE	252	224
IR	13.93	29.86
IRR (95% CI)	ref	2.14 (1.78 to 2.58)
PY for first serious AE	2508	1328
No. of serious AE	29	68
IR	1.16	5.12
IRR (95% CI)	ref	4.43 (2.83 to 7.09)
PY for first infection	2458	1167
No. of infection	40	100
IR	1.63	8.57
IRR (95% CI)	ref	5.27 (3.62 to 7.80)
PY for first serious infection	2557	1371
No. of serious infection	8	34
IR	0.31	2.48
IRR (95% CI)	ref	7.93 (3.60 to 19.83)

*Including follow-up time before 1st bDMARD (n=1403)
PY: person-years; IR: incident rate per 100 person years; IRR: incident rate ratio; 95% CI: 95% confidence interval.

biologic group (IR=18.8). The corresponding IRR became 1.89 (95% CI: 1.68–2.13). When only the follow-up time up until the first AE in both treatment groups was counted in, the median follow-up until first AE was 10 months in the "DMARDs only" group and 13 months in the biologic group (data not shown). The corresponding IRR for the biologic group was 2.14 (95% CI: 1.78–2.58). For the secondary outcomes the respective IRRs were 4.43 (95% CI: 2.83–7.09) for first serious AE, 5.27 (95% CI: 3.62–7.80) for first infection and 7.93 (95% CI: 3.60 –19.83) for first serious infection. Supplementary Table I illustrates the type of infections and adverse events in both groups.

Association of the treatment group with the risk of first AE

The KM plots (Fig. 1) depicted that the risk of first AE or infection (irrespective of severity) was significantly

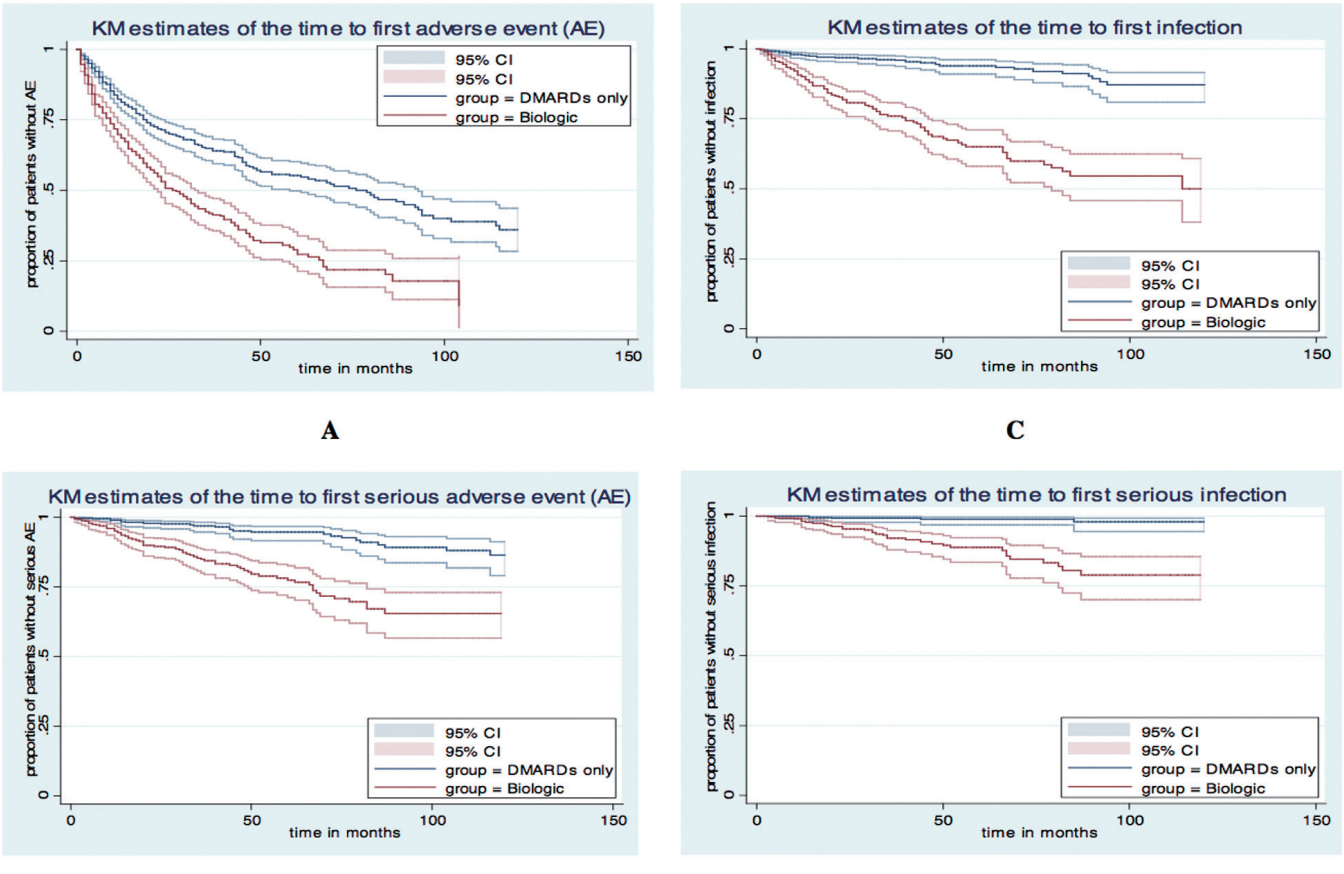
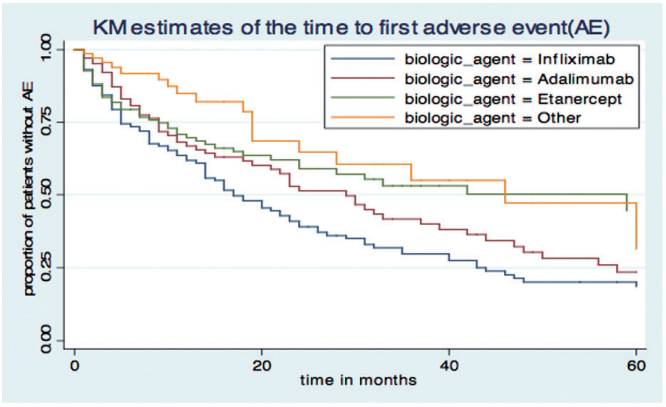


Fig. 1. Kaplan-Meier plots depicting the fraction of patients from the time from onset of first treatment (sDMARD or bDMARD) until the first adverse or serious adverse event (**A**, **B** respectively) and the first infection or serious infection (**C**, **D** respectively) (in months)

Table III. Mutually adjusted hazard ratios (HR) and 95% confidence intervals (95%CI) of the risk of the first adverse event (of any severity), by the indicated variables.

	Adverse event (476 events)			Serious adverse event (97 events)			Infection (140 events)			Serious infection (42 events)		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Treatment group												
sDMARDs only	ref			ref			ref			ref		
bDMARDs	1.98	1.64 to 2.39	<0.001	3.95	2.52 to 6.21	<0.001	5.01	3.41 to 7.35	<0.001	6.86	3.06 to 15.4	<0.001
Extra-articular manifestations												
No	ref			ref			ref			ref		
Yes	1.29	1.05 to 1.60	0.018	1.39	0.80 to 2.40	0.240	1.54	0.99 to 2.40	0.057	1.51	0.61 to 3.75	0.379
Co-morbidities												
No	ref			ref			ref			ref		
Yes	1.19	0.98 to 1.44	0.077	1.54	1.00 to 2.36	0.050	1.28	0.89 to 1.83	0.177	1.19	0.62 to 2.27	0.599
missing/unknown	1.02	0.73 to 1.43	0.912	1.04	0.48 to 2.27	0.914	1.25	0.71 to 2.19	0.443	1.00	0.33 to 3.02	0.994
Initial DAS-28												
>5.2	ref			Ref			ref			ref		
3.1 to 5.2	0.80	0.66 to 0.97	0.026	0.97	0.63 to 1.48	0.897	0.99	0.70 to 1.40	0.964	1.10	0.57 to 2.12	0.766
2.6 to 3.1	0.54	0.31 to 0.92	0.024	2.26	0.94 to 5.41	0.067	1.19	0.51 to 2.76	0.693	4.78	1.58 to 14.48	0.006
≤2.6	0.89	0.57 to 1.39	0.615	0.33	0.05 to 2.46	0.281	0.50	0.15 to 1.61	0.246	1.01	0.13 to 7.91	0.992
Total dose of steroids (mg)												
<500	ref			ref			ref			ref		
≥500	1.22	0.94 to 1.58	0.133	1.15	0.71 to 1.85	0.571	1.05	0.69 to 1.57	0.832	1.62	0.83 to 3.16	0.158
none	0.84	0.63 to 1.11	0.211	0.25	0.08 to 0.79	0.018	0.70	0.38 to 1.29	0.250	0.20	0.03 to 1.50	0.116



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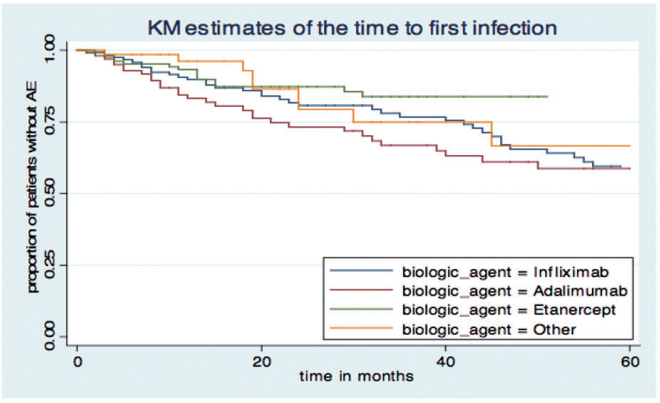

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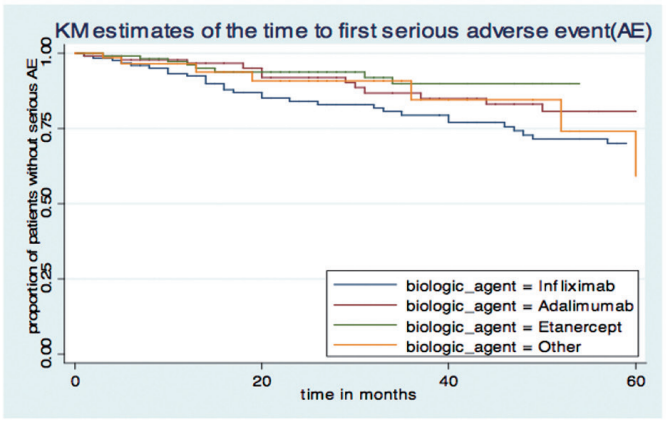

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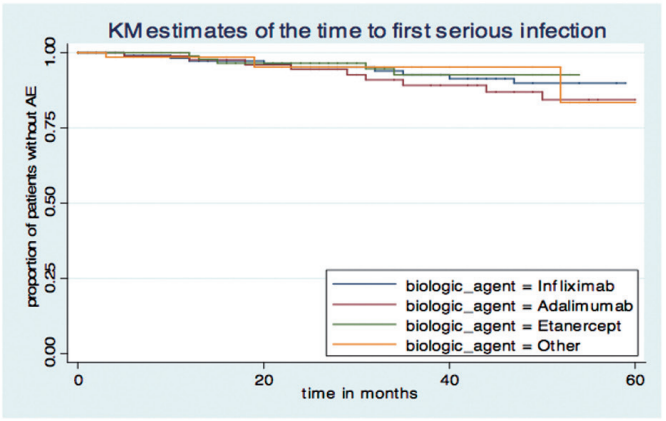

D

Fig. 2. Kaplan-Meier plots depicting the fraction of patients from the time from onset of first specific biologic treatment (bDMARD) until the first adverse or serious adverse event (**A**, **B** respectively) and the first infection or serious infection (**C**, **D** respectively) (in months).

Table IV. Crude and mutually adjusted hazard ratios (HR) and 95% confidence intervals (95%CI) of the risk of the first adverse event (of any severity) by different bDMARD taken at baseline.

n=434	Adverse event (224 events)		Serious adverse event (68 events)		Infection (100 events)		Serious infection (34 events)	
	HR	*p*	HR	*p*	HR	*p*	HR	*p*
Crude								
Infliximab	ref		ref		ref		ref	
Adalimumab	0.78	0.129	0.57	0.071	1.19	0.457	1.09	0.826
Etanercept	0.62	0.005	0.38	0.011	0.58	0.065	0.60	0.332
Other	0.43	0.001	0.84	0.663	0.81	0.560	1.22	0.727
Mutually adjusted*								
Infliximab	ref		ref		ref		ref	
Adalimumab	0.84	0.292	0.54	0.058	1.19	0.463	1.10	0.819
Etanercept	0.67	0.032	0.39	0.019	0.63	0.140	0.72	0.559
Other	0.45	0.003	0.69	0.370	0.77	0.481	0.97	0.958

*After controlling for the following potential confounders: extra-articular manifestations, co-morbidities, initial DAS-28 and total dose of steroids.

higher for the biologic group (all *p*-values from logrank tests <0.001). The bivariate Cox proportional-hazards models showed that none of the potential confounders appeared to alter the hazard ratio (HR) of the main exposure (treatment group) by more than 6%. The highest relative change (5.6%) was observed for total dose of steroids (unadjusted HR for treatment group was 2.03; HR after adjustment for total dose of steroids was 1.92). In parallel, extra-articular manifestations, co-morbidities, increased initial DAS-28 and total steroid dose ≥500 mg were significantly associated with a higher risk of first AE (data not shown). When introducing the four aforementioned variables as potential confounders into the Cox models, the association of treatment group with a risk of any AE which occurred first (primary outcome) remained substantially statistically significant with the corresponding HR for the biologic group compared to the "DMARDs only" group being 1.98 (95% CI: 1.64 –2.39, Table III). More specific, the risk of first AE (when compared to the referent "DMARDs only" group) was substantially higher for those individuals switching to other biologics (adjusted HR=2.56, 95% CI: 2.03–3.24) than for those receiving only one biologic agent (HR=1.62, 95% CI: 1.29–2.04).

For the secondary outcomes the adjusted HRs contrasting patients in the biologic group with those in the "DMARDs only" group were 3.95 (95% CI: 2.52–6.21) for serious AE, 5.01 (95% CI: 3.41–7.35) for infection and 6.86 (95% CI: 3.06–15.41) for serious infection (data not shown). When individuals with less than 6 months of follow-up were excluded (318 cases, 23%, data not shown) the aforementioned results essentially did not alter.

Comparison of specific bDMARDs

The subgroup analysis for the comparison across specific biologic agents is presented in Figure 2 and Table IV. KM plots and univariate Cox analysis revealed that patients in the biologic group initially treated with infliximab (and adalimumab to a lesser extent) had a higher risk of any AE when compared to patients receiving initially etanercept or other bDMARDs. In the analyses of the secondary outcomes and especially when the event was the first infection (or serious infection), those treated with adalimumab had a somewhat higher risk. These results were slightly less pronounced when controlling for potential confounders (Table IV).

Methotrexate and adverse events

We further examined the potential association of mean MTX dose with the risk of first AE when restricting the sample to those individuals treated only with MTX (681 patients with available information on dose quantity). The average dose of MTX was 10.7 mg (±1.9). A dichotomous variable was constructed: mean MTX dose of 10 or higher (561 patients, referent category) *vs*. below 10 mg (120 patients). Those with a dose below 10 mg had a significantly higher risk of any AE when compared to those with higher doses (HR=1.55, 95% CI: 1.12–2.13, *p*=0.008) (data not shown).

Discussion

We have found that the risk of any AE, irrespective of severity, was significantly increased in RA patients treated with bDMARDs, compared to those taking sDMARDs. Half of patients with bDMARDs had at least one AE during their observation and the adjusted HR contrasting those treated with bDMARDs with those receiving sDMARDs was 1.98 (95% CI: 1.64–2.39). Patients treated with infliximab and adalimumab were more likely to suffer from any AE compared to other bDMARD, whereas adalimumab offered a slightly higher risk for infections in specific. Higher doses of MTX did not increase the risk for AEs.

Our findings are in line with previous evidence derived from controlled studies or registries, indicating higher risks of serious infections, tuberculosis, herpes zoster, skin and soft tissue infections and pneumonia from common pathogens or opportunistic infections, associated with biologics (8, 11-18). Associations between anti-TNF-α treatment and Guillain-Barré syndrome, autoimmune diseases, interstitial lung disease and psoriasis were described (19-21). The risk for lymphoma, skin cancer, melanoma or non-melanoma tumours in patients receiving anti-TNF-α therapy was described and considered as a dose-dependent phenomenon (22-27).

On the contrary, many studies suggest that biologic treatment is equally safe to conventional therapy (28-30). Biologics and especially anti-TNF-α agents were not associated with increased risk of pneumonia, other serious skin or soft tissue infections or reactivation of viral hepatitis, even by considering the observation time after instituting of these agents (31-37). The risk of lymphoma, other malignancies, demyelinating dis-

ease, acute coronary syndrome or overall mortality was not increased with biologics (38-44). An explanation for these discrepancies probably lies around in the field of study design, or the clinical practice adopted by each centre that offers data to national registries.

Studies have shown that apart from therapy, co-morbidities, high disease activity (HDA) and the use of glucocorticoids may contribute to AEs and particularly to infections (45-50). RA in Greek patients is milder than in Northern Europeans and the sex-, age, and disease duration adjusted rates of remission in Greek patients were the highest among patients from other European countries, thus the side effects should be attributed to therapy, rather than to disease activity (51, 52). The milder course of the disease could partially explain the lower incidence rates of AEs, especially those of serious infections, compared to previous reports (2.48/100PY in the biologics group and 0.31/100PY in the DMARDs group compared to 5-6/100PY in the biologics generally) (53). On the other hand the above data raise the question whether our patients have been over-treated with biologics. This is not probably the case since only 31% of our patients received biologics and only 10% of them did so within the first 3 months of treatment, implying that the patients have not been treated aggressively.

Strengths of the study were its long duration of observation and the level of detail including the continuous recording of complete information (comorbidities, switching of therapy and unpredictable factors that affect doctor's judgment) about patients' condition and treatment, biologic or conventional, which allowed us to provide a clear, real-world picture of RA patients. The retrospective nature, missing data of the HAQ scores and the small mean dose of MTX favouring better outcomes in terms of AEs, were among the limitations. Previous studies showed that high doses of MTX were related to more frequent and serious AEs while lower doses showed a favourable long-term safety (54, 55). Nevertheless, our sDMARD treatment results (remission 30.7%, low disease activity 20.3%, medial disease activity 22% and HDA 27%) were comparable to that of prospective studies and in particular the MASCOT study, avoiding administration of high doses of MTX (56). Another limitation, finally, was that patients were classified into disease groups, as operationally defined, based on the information collected only after their initial visit at the university hospital, meaning that there could be a left-censoring bias since we were not aware of the potential occurrence of any AEs prior to their entry to the study.

Conclusions

Biologic agents were more likely to increase the risk of any AE (irrespective of severity), in patients with RA and should be carefully administered after consideration of the possible risks and benefits for each patient. Nevertheless, in one third of RA patients with severe disease, the benefits of biologic treatments probably overweigh the risks for AEs. Further research is needed to investigate the equilibrium between effectiveness and toxicity across biologic agents or to examine whether early drug treatment could be beneficial.

References

1. SOLOMON DH, KARLSON EW, RIMM EB *et al*.: Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation* 2003; 107: 1303-7.
2. BATHON JM, MARTIN RW, FLEISCHMANN RM *et al*.: A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000; 343: 1586-93.
3. LIPSKY PE, VAN DER HEIJDE DM, ST CLAIR EW *et al*.: Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000; 343: 1594-602.
4. WEINBLATT ME, KEYSTONE EC, FURST DE *et al*.: Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum* 2003; 48: 35-45.
5. DADOUN S, ZEBOULON-KTORZA N, COMBES-CURE C *et al*.: Mortality in rheumatoid arthritis over the last fifty years: systematic review and meta-analysis. *Joint Bone Spine* 2013; 80: 29-33.
6. ZHANG N, WILKINSON S, RIAZ M, ÖSTÖR, AJ, NISAR MK: Does methotrexate increase the risk of varicella or herpes zoster infection in patients with rheumatoid arthritis? A systematic literature review. *Clin Exp Rheumatol* 2012; 30: 962-71.
7. KOURBETI IS, ZIAKAS PD, MYLONAKIS E: Biological therapies in rheumatoid arthritis and the risk of opportunistic infections: A meta-analysis. *Clin Infect Dis* 2014; [In press].
8. RAMIRO S, GAUJOUX-VIALA C, NAM JL *et al*.: Safety of synthetic and biological DMARDs: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis* 2014; 73: 529-35.
9. LISTING J, KEKOW J, MANGER B *et al*.: Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNF-α inhibitors and rituximab. *Ann Rheum Dis* 2013; 73: 149-53.
10. GARDAM MA, KEYSTONE EC, MENZIES R *et al*.: Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. *Lancet Infect Dis* 2003; 3: 148-55.
11. DIXON WG, WATSON K, LUNT M, HYRICH KL, SILMAN AJ, SYMMONS DP: Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2006; 54: 2368-76.
12. STRANGFELD A, LISTING J, HERZER P *et al*.: Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. *JAMA* 2009; 301: 737-44.
13. SALLIOT C, GOSSEC L, RUYSSEN-WITRAND A *et al*.: Infections during tumour necrosis factor-alpha blocker therapy for rheumatic diseases in daily practice: a systematic retrospective study of 709 patients. *Rheumatology* (Oxford) 2007; 46: 327-34.
14. GREENBERG JD, REED G, KREMER JM *et al*.: Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. *Ann Rheum Dis* 2010; 69: 380-6.
15. DIXON WG, HYRICH KL, WATSON KD, LUNT M, GALLOWAY J, USTIANOWSKI A: Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). *Ann Rheum Dis* 2010; 69: 522-8.
16. GALLOWAY JB, HYRICH KL, MERCER LK *et al*.: Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatology* (Oxford) 2011; 50: 124-31.
17. CURTIS JR, PATKAR N, XIE A *et al*.: Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. *Arthritis Rheum* 2007; 56: 1125-33.
18. MARIETTE X, GOTTENBERG JE, RAVAUD P, COMBE B: Registries in rheumatoid arthritis and autoimmune diseases: data from the French registries. *Rheumatology* (Oxford) 2011; 50: 222-9.
19. RAMOS-CASALS M, BRITO-ZERÓN P, MUÑOZ

S *et al*.: Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. *Medicine* (Baltimore) 2007; 86: 242-51.
20. PEREZ-ALVAREZ R, PEREZ-DE-LIS M, DIAZ-LAGARES C *et al*.: Interstitial lung disease induced or exacerbated by TNF-targeted therapies: analysis of 122 cases. *Semin Arthritis Rheum* 2011; 41: 256-64.
21. HARRISON MJ, DIXON WG, WATSON KD *et al*.: Rates of new-onset psoriasis in patients with rheumatoid arthritis receiving anti-tumour necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis* 2009; 68: 209-15.
22. ZINTZARAS E, VOULGARELIS M, MOUTSOPOULOS HM: The risk of lymphoma development in autoimmune diseases: a meta-analysis. *Arch Intern Med* 2005; 165: 2337-44.
23. MARIETTE X, TUBACH F, BAGHERI H *et al*.: Lymphoma in patients treated with anti-TNF: results of the 3-year prospective French RATIO registry. *Ann Rheum Dis* 2010; 69: 400-8.
24. GEBOREK P, BLADSTRÖM A, TURESSON C *et al*.: Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. *Ann Rheum Dis* 2005; 64: 699-703.
25. WOLFE F, MICHAUD K: Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. *Arthritis Rheum* 2004; 50: 1740-51.
26. WOLFE F, MICHAUD K: Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. *Arthritis Rheum* 2007; 56: 2886-95.
27. BONGARTZ T, SUTTON AJ, SWEETING MJ, BUCHAN I, MATTESON EL, MONTORI V: 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. *JAMA* 2006; 295: 2275-85.
28. VAN DE PUTTE LB, ATKINS C, MALAISE M *et al*.: Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Ann Rheum Dis* 2004; 63: 508-16.
29. WEISMAN MH, PAULUS HE, BURCH FX *et al*.: A placebo-controlled, randomized, double-blinded study evaluating the safety of etanercept in patients with rheumatoid arthritis and concomitant comorbid diseases. *Rheumatology* (Oxford) 2007; 46: 1122-5.
30. WIENS A, CORRER CJ, VENSON R, GROCHOCKI MC, OTUKI MF, PONTAROLO R: A meta-analysis of the efficacy and safety of using infliximab for the treatment of rheumatoid arthritis. *Clin Rheumatol* 2009; 28: 1365-73.
31. WOLFE F, CAPLAN L, MICHAUD K: Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. *Arthritis Rheum* 2006; 54: 628-34.
32. GALLOWAY JB, MERCER LK, MOSELEY A *et al*.: Risk of skin and soft tissue infections (including shingles) in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis* 2013; 72: 229-34.
33. ROUX CH, BROCQ O, BREUIL V, ALBERT C, EULLER-ZIEGLER L: Safety of anti-TNF-alpha therapy in rheumatoid arthritis and spondylarthropathies with concurrent B or C chronic hepatitis. *Rheumatology* (Oxford) 2006; 45: 1294-7.
34. SCHNEEWEISS S, SETOGUCHI S, WEINBLATT ME *et al*.: Anti-tumor necrosis factor alpha therapy and the risk of serious bacterial infections in elderly patients with rheumatoid arthritis. *Arthritis Rheum* 2007; 56: 1754-64.
35. KIEVIT W, FRANSEN J, ADANG EM *et al*.: Long-term effectiveness and safety of TNF-blocking agents in daily clinical practice: results from the Dutch Rheumatoid Arthritis Monitoring register. *Rheumatology* (Oxford) 2011; 50: 196-203.
36. GRIJALVA CG, KALTENBACH L, ARBOGAST PG, MITCHEL EF JR, GRIFFIN MR: Initiation of rheumatoid arthritis treatments and the risk of serious infections. *Rheumatology* (Oxford) 2010; 49: 82-90.
37. CANTINI F, BOCCIA S, GOLETTI D *et al*.: HBV reactivation in patients treated with antitumor necrosis factor-alpha (TNF-α) agents for rheumatic and dermatologic conditions: a systematic review and meta-analysis. *Int J Rheumatol* 2014; 2014: 926836.
38. ASKLING J, FORED CM, BAECKLUND E *et al*.: Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. *Ann Rheum Dis* 2005; 64: 1414-20.
39. DREYER L, MELLEMKJÆR L, ANDERSEN AR *et al*.: Incidences of overall and site specific cancers in TNF-α inhibitor treated patients with rheumatoid arthritis and other arthritides - a follow-up study from the DANBIO Registry. *Ann Rheum Dis* 2013; 72: 79-82.
40. LOPEZ-OLIVO MA, TAYAR JH, MARTINEZ-LOPEZ JA *et al*.: Risk of malignancies in patients with rheumatoid arthritis treated with biologic therapy: a meta-analysis. *JAMA* 2012; 308: 898-908.
41. THOMPSON AE, RIEDER SW, POPE JE: Tumor necrosis factor therapy and the risk of serious infection and malignancy in patients with early rheumatoid arthritis. *Arthritis Rheum* 2011; 63: 1479-85.
42. CRUZ FERNÁNDEZ-ESPARTERO M, PÉREZ-ZAFRILLA B, NARANJO A *et al*.: Demyelinating disease in patients treated with TNF antagonists in rheumatology: data from BIOBADASER, a pharmacovigilance database, and a systematic review. *Semin Arthritis Rheum* 2011; 41: 524-33.
43. LJUNG L, SIMARD JF, JACOBSSON L, RANTAPÄÄ-DAHLQVIST S, ASKLING J: Treatment with tumor necrosis factor inhibitors and the risk of acute coronary syndromes in early rheumatoid arthritis. *Arthritis Rheum* 2012; 64: 42-52.
44. LUNT M, WATSON KD, DIXON WG: No evidence of association between anti-tumor necrosis factor treatment and mortality in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2010; 62: 3145-53.
45. BAECKLUND E, ILIADOU A, ASKLING J *et al*.: Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. *Arthritis Rheum* 2006; 54: 692-701.
46. AU K, REED G, CURTIS JR *et al*.: High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. *Ann Rheum Dis* 2011; 70: 785-91.
47. VAN DARTEL SA, FRANSEN J, KIEVIT W *et al*.: Predictors for the 5-year risk of serious infections in patients with rheumatoid arthritis treated with anti-tumour necrosis factor therapy: a cohort study in the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry. *Rheumatology* (Oxford) 2013; 52: 1052-7.
48. DIXON WG, ABRAHAMOWICZ M, BEAUCHAMP ME *et al*.: Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case–control analysis. *Ann Rheum Dis* 2012; 71: 1128-33.
49. LISTING J, KEKOW J, MANGER B *et al*.: Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNF-α inhibitors and rituximab. *Ann Rheum Dis* 2015; 74: 415-21.
50. EMERY P, GALLO G, BOYD H *et al*.: Association between disease activity and risk of serious infections in subjects with rheumatoid arthritis treated with etanercept or disease-modifying anti-rheumatic drugs. *Clin Exp Rheumatol* 2014; 32: 653-60.
51. DROSOS AA, LANCHBURY JS, PANAYI GS, MOUTSOPOULOS HM: Rheumatoid arthritis in Greek and British patients. A comparative clinical, radiologic and serologic study. *Arthritis Rheum* 1992; 35: 745-8.
52. SOKKA T, HETLAND ML, MÄKINEN H *et al*.: Remission and rheumatoid arthritis: data on patients receiving usual care in twenty-four countries. *Arthritis Rheum* 2008; 58: 2642-51.
53. DIXON WG, SYMMONS DP, LUNT M, WATSON KD, HYRICH KL, SILMAN AJ: Serious infection following anti-tumor necrosis factor alpha therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies. *Arthritis Rheum* 2007; 56: 2896-904.
54. VERSTAPPEN SM, BAKKER MF, HEURKENS AH *et al*.: Adverse events and factors associated with toxicity in patients with early rheumatoid arthritis treated with methotrexate tight control therapy: the CAMERA study. *Ann Rheum Dis* 2010; 69: 1044-8.
55. BURMESTER GR, KIVITZ AJ, KUPPER H *et al*.: Efficacy and safety of ascending methotrexate dose in combination with adalimumab: the randomised CONCERTO trial. *Ann Rheum Dis* 2014 Feb 18 [Epub ahead of print].
56. CAPELL HA, MADHOK R, PORTER DR *et al*.: Combination therapy with sulfasalazine and methotrexate is more effective than either drug alone in patients with rheumatoid arthritis with a suboptimal response to sulfasalazine: results from the double-blind placebo-controlled MASCOT study. *Ann Rheum Dis* 2007; 66: 235-41.