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RESEARCH ARTICLE

Ten Year Risk of Cardiovascular Events during anti-TNF Alpha in Rheumatoid Arthritis Patients

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Abstract

Objective: To analyze the rate of major CV events in 433 patients with longstanding RA, treated for more than 10 years with anti-TNFα or DMARDs.

Methods: All RA patients treated with anti-TNF-α from 2000 and 2002 (n. 86; TNF+ group) and a random sample of 258 patients treated with DMARDs out of 829 followed-up in the same period in the same Unit (TNF- group) were analyzed. Myocardial infarction, heart failure, stroke, transient cerebral ischemic attack were considered. Exposure (anti-TNF-α vs. DMARDs) and outcome (CV events) were analyzed by the proportional hazard Cox regression, adjusting for RA duration, DAS 28, seropositivity (RF, anti CCP), treatment and Framingham CV risk factors (adjusted according to EULAR recommendations).

Results: CV events were detected in 18.9% of cases with an incidence rate of 2.4% patients/year (95%CI: 1.5-3.7) in TNF+ and 1.3% patients/year (95%CI: 0.9-1.7) in TNF- group. Events occurred after a mean of 8.3 ± 3.6 years of anti-TNF exposure and 13.3 ± 8 years of DMARDs exposure (p: 0.006). Cox analysis, adjusted for sex, age, CV risk factors, DAS28, FR positivity, corticosteroids, anti-inflammatory drugs and methotrexate treatment, showed that only Framingham risk score is slightly associated with CV events (HR: 1.03, 95%CI: 1.01-1.06). In addition, diabetes (p: 0.017) and coronary artery disease (p: 0.015) were associated with myocardial infarction, while higher age at RA onset (p: 0.02) and Framingham risk score (p: 0.0008) were associated with heart failure.

Conclusions: CV events occurred in 2.4% patient/year during anti-TNF alpha treatment. A strict cardiovascular monitoring was mandatory in order to prevent major CV events.

Keywords

Rheumatoid arthritis, Cardiovascular disease, Anti-TNF alfa, Myocardial infarction, Heart failure, Long-standing disease, Framingham risk factors

Introduction

Rheumatoid arthritis (RA) is a chronic and systemic inflammatory disease, characterized by an increased risk of premature death, largely due to cardiovascular disease (CVD) and particularly to coronary artery disease (CAD) [1,2]. In addition to classical Framingham CV risk factors, the inflammatory burden of the disease leads to the development of early and accelerated atherosclerosis [3,4], mediated by cytokines, immune complex, abnormal lipid metabolism and endothelial dysfunction [5,6]. Systemic inflammation is associated with endothelial damage, directly with depletion of circulating endothelial cell progenitors [7] or indirectly by the accentuation of multiple risk pathways including lipid abnormalities [8] and insulin-resistance [9]. The

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introduction of anti-Tumor Necrosis Factor (TNF alpha treatment has improved the clinical outcome of RA suppressing systemic inflammation. Recently, different studies investigated the effect of TNF alpha blockers also in modify the cardiovascular risk profile [10-12]. TNF alpha, as many other inflammatory cytokines, is directly involved in all the stages of atherosclerosis, including modification of lipid profile, insulin-resistance, plaque formation and rupture, the most common event leading to acute myocardial infarction (MI) [13]. A protective role of anti-TNF alpha treatment has been reported for MI, especially in a subset of patients who responded to treatment, suggesting that its CV protection could be dependent on its ability to reduce systemic inflammation [14]. In addition, a significantly decreased risk in CAD incidence was confirmed by other authors [15-17], while the protective effect on ischemic stroke is not so clearly established [18].

The aim of this study is to analyses the prevalence and risk factors of CV events occurrence in a monocentric cohort of patients treated with anti-TNF alpha blockers followed up for a long period, comparing with patients treated non-biologic disease-modifying anti rheumatic drugs (DMARDs).

Patients and Methods

Patients: we retrospectively analyzed clinical charts of 86 consecutive patients affected by RA, that underwent biological treatment between January 2000 and December 2002 (defined as group TNF+). At that time, anti-TNF alpha drugs included only Infliximab and Etanercept. As control group, we considered 258 RA outpatients, randomly chosen on 829 RA cases, followed-up in the same period in the same Rheumatology Unit (defined as Group TNF-). Group TNF- patients received treatment with traditional DMARDs, namely methotrexate, hydroxychloroquine, sulfasalazine. RA patients fulfilled both the 1997 ACR criteria [19] and 2010 EULAR/ACR criteria retrospectively applied [20].

Study design: baseline data are considered as clinical data collected at the first administration of the anti-TNF alpha drug (TNF+ group) or the first clinical observation (TNF- group). Data collected at the last available clinical evaluation or at the occurrence of a CV event for both groups, was considered as the last evaluation available.

Methods

Demographic, clinical and laboratory data were extracted from clinical records. At first visit, disease activity indexes (ESR, -reactive protein, DAS28, SDAI), immunological data (rheumatoid factor, anti-CCP , anti-nuclear antibodies), treatment (steroid, methotrexate, other DMARDs, non-steroid anti-inflammatory drugs or anti-TNF alpha) and traditional CV risk factors (hypertension, smoking habits, hypercholesterolemia, hyper-trygliceridemia, diabetes mellitus, familiar history of CVD) were recorded. CV risk assessment was retrospectively calculated using Framingham score, adjusted for RA duration, RF or anti-CCP positivity or extra-articular complications, according to EULAR recommendations [21]. Incident CV events were defined as acute MI, CAD (accounted also as any surgical or percutaneous revascularization procedure), heart failure, pulmonary hypertension, ischemic stroke, occurred after the diagnosis of RA. We excluded any CV event occurred before RA diagnosis. We did not consider atrial fibrillation as a CV event. CV event were recorded from medical records or from hospitalization registry. Single event features were subsequently reviewed, according to standardized definitions [22].

Statistical analysis

Baseline differences between the two cohorts were tested using t-test or Wilcoxon's rank sum test for continuous variables according to the variable distribution and the chi-square test for categorical variables. Probability of CV event occurrence was estimated as incident rates (IR) and 95% confidence intervals (CI).

The association between TNF exposure and the occurrence of CV events was analyzed using Cox proportional hazard regression model and presented as hazard ratios (HR) and 95% Cis. The same analyses were repeated adjusting for potential baseline confounders: sex, RA duration, baseline DAS28, seropositivity (RF or anti CCP), DMARD treatment, glucocorticoid use and Framingham CV risk factors (adjusted according to EULAR recommendations). All the a priori confounders were entered and retained in the model regardless of their statistical significance.

All analyses were conducted using Stata V.11 StataCorp, College Station, Texas, USA.

Results

The eighty-six TNF+ patients showed a mean age at RA onset of 31.5 years (SD: 12.9), a mean duration of disease before starting anti-TNF alpha (22.7 years, SD: 7.6) and a mean duration of RA until the last evaluation of 23.2 years (SD: 7.2). Demographic and clinical data of TNF+ and TNF- are shown in Table 1. Comparing with TNF- group, TNF+ patients showed lower age at RA onset ($p < 0.0001$), longer follow-up duration ($p < 0.0001$). At the moment of anti-TNF alpha starting, they showed active disease, with a mean DAS 28 of 5.5 (SD: 1.3) and mean SDAI of 38.9 (SD: 16.6). CV events occurred in 21 TNF+ patients (24.4%) and in 44 TNF- (17%): the mean duration of drug exposure resulted be lower in TNF+ group (8.3 years; SD: 3.6) compared with TNF- (13.3 years; SD: 7.9) (p: 0.006) (Table 2).

As expected, TNF+ patients more frequently used non-steroidal anti-inflammatory drugs ($p = 0.005$), methotrexate ($p = 0.004$), corticosteroids (p: 0.018) and corticosteroids at dosage > 5 mg/day ($p < 0.0001$) when compared with TNF- cases. By contrast, hydroxychlo-

Table 1: Demographic and clinical data of 86 patients treated with anti-TNF alfa (TNF+) and 258 patients treated with DMARDs (TNF-).

Characteristics		TNF+ (n. 86)	TNF- (n. 258)	p
Demographics				
	F/M	68/18	200/58	0.88
	Mean age at onset, years (SD)	31.5 (12.9)	51.67 (12.9)	< 0.0001[a]
	Mean RA duration at last evaluation, years (SD)	23.2 (7.2)	17.3 (8.7)	< 0.0001[a]
	Mean RA duration at CV event, years (SD)	18.9 (8.2)	13.3 (7.9)	0.015[a]
	Mean duration of drug exposure, years (SD)	9.69 (4.47)	13.9 (6.6)	< 0.0001[a]
	Mean duration of drug exposure until CV event, years (SD)	8.3 (3.6)	13.3 (7.9)	0.006[a]
	RF (%)	57/83 (68.7%)	177/256 (69.1%)	1.0
	Anti CCP (%)	11/14 (78%)	59/91 (64.8%)	0.06
Comorbidities				
	Arterial hypertension (%)	29 (33.7)	29/107 (27)	0.34
	Smoking habits (%)	22 (25.6)	30/113 (26.5)	1.0
	Dyslipidemia	7 (8)	15/104 (14.4)	0.36
	Familiar CV disease (%)	30 (34.8)	111 (43)	0.22
	Diabetes (%)	4 (4.6)	6/108 (5.6)	1.0
	Coronaropathy (%)	3 (3.5)	4 (1.5)	0.37
	Mean n. Framingham risk factors (SD)	5.6 (6.8)	7.3 (8.3)	0.18[b]
RA-related drugs				
	NSAIDs	63 (73.2%)	145 (56%)	0.005
	Methotrexate	71/86 (82.5%)	170 (65.8%)	0.004
	Hydroxychloroquine	18/86 (20.9%)	97 (37.6%)	0.005
	Prednisone	79/86 (91.8%)	209 (81%)	0.018
	Prednisone > 5 mg/day	32/84 (38%)	14/257 (5.4%)	< 0.0001
CV-related drugs	B blockers	14/85 (16.2%)	59/258 (22.8%)	0.2
	Ca antagonists	9/85 (10.5%)	34/258 (13.2%)	0.7
	Ace inhibitors	26/85 (30.5%)	65/258 (25.2%)	0.3
	Diuretics	16/85 (18.8%)	35/257 (13.6%)	0.3
	Anti-platelets	21/86 (24.4%)	71/258 (6.6%)	0.6
	Oral anti-coagulants	5/86 (5.8%)	14/258 (5.4%)	1.0
	Statins	7/86 (8.1%)	36/258 (13.9%)	0.2

NSAIDs: non-steroidal anti-inflammatory drugs; RF: Rheumatoid Factor; [a] = Unpaired t test; [b] = Mann Whitney test.

Table 2: Incident rate of CV events in 86 patients treated with anti-TNF alfa (TNF+) and 258 patients treated with DMARDs (TNF-).

Exposure	n. patients	Patient-years (×100)	CV events/100 patients/year
TNF+	86	855.87	2.4
TNF-	258	3452.62	1.27

roquine was more frequently used in TNF- group (p = 0007).

During follow-up CV events occurred in 65 cases (18.9%): MI (in 28 cases: 43%), heart failure (in 14 cases: 21.6%), TIA (in 7 cases: 10.8%), ischemic heart disease (in 4 cases: 6.2%), cerebral haemorrhages (3: 4.6%), acute pulmonary oedema and advanced AV block requiring with pacemaker implant in 1 case each (1.5%). CV events occurred after a mean of 15 years (SD: 8.3) and after a mean duration of drug exposure of 11.7 years (SD: 7.2).

No difference in event distribution was found between two groups: an incident rate of 2.4/100 person/year (95%CI: 1.5-3.7) occurred in TNF+ and 1.27 events/100 person/year (95%CI: 0.9-1.7) in TNF- group, with a incidence rate ratio of 1.92 (95%CI: 1.08-3.3). Clinical data of 65 patients with CV events and 279 cases without CV events were shown in Table 3.

Patients with CV events more frequently showed at baseline arterial hypertension (p: 0.03), dyslipidemia (p < 0.0001), diabetes (p < 0.0001), familiar CV diseases (p < 0.0001) and CAD (p: 0.005). No significant differences in RF (39.8% vs. 68.8%) or anti-CCP (82.3% vs. 63.6%) seropositivity, RA activity indexes (DAS 28), ESR or C-reactive protein levels were found.

Cox analysis, corrected for sex, age, CV risk factors, DAS28, FR positivity, corticosteroids, anti-inflammatory drugs and methotrexate, showed that only Framingham risk score is slightly associated with CV events (HR: 1.03, 95%CI: 1.01-1.06). Anti-TNF alpha exposure showed a wide dispersion data to draw conclusions (HR: 1.8; 95%CI: 0.8-3.9). An incidence of MI of 14.5% patient/year and 7.8% patient/year was observed in TNF+ and

Table 3: Demographic and clinical data in 65 patients with CV event and 279 patients without CV events.

Characteristics		With CV events (n. 65)	Without CV events (n. 279)	p
Demographics	F/M	43/22	224/55	0.02
	Mean age at onset, years (SD)	54.4 (12.3)	45.7 (15.6)	< 0.0001[a]
	Mean age at baseline, years (SD)	60.8 (10)	54.3 (11.9)	< 0.0001[a]
	Mean drug exposure duration, years (SD)	14.3 (6.9)	18.4 (8.8)	0.04[a]
	Mean RA duration at last observation, years (SD)	18.7 (7.1)	18.4 (8.8)	0.84[a]
	Anti-TNF alfa exposure, n. (%)	21/65 (32)	65/214 (30.3)	0.76
Comorbidities	Arterial hypertension (%)	17/37 (45.9)	41/156 (26.2)	0.032
	Smoking habits (%)	10/35 (28.5)	37/156 (23.7)	0.56
	Dyslipidemia (%)	24/65 (36.9)	17/153 (11.1)	< 0.0001
	Familiar CV disease (%)	45/65 (69.2)	113/279 (40.5)	< 0.0001
	Diabetes (%)	10/43 (23.2)	7/156 (4.4)	< 0.0001
	CAD (%)	4/38 (10.5)	4/279 (1.4)	0.005
	Mean n. Framingham risk factors at the CV event (SD)	12.7 (11.47)	5.98 (7.2)	< 0.0001[b]
CV-related drugs	B blockers (%)	29 (44.6)	44/278 (15.8)	< 0.0001
	Ace inhibitors (%)	29 (44.6)	42/278 (15.1)	< 0.0001
	Diuretics (%)	25 (38.4)	48/278 (17.2)	< 0.0001
	Anti-platelets (%)	39 (60)	53/279 (18.9)	< 0.0001
	Oral anti-coagulants (%)	12 (18.4)	7/279 (2.5)	< 0.0001
	Statins (%)	18 (27.6)	25/279 (8.9)	< 0.0001

[a] = Unpaired t test; [b] = Mann-Whitney test.

Table 4: Incident rate of MI and heart failure in 86 patients treated with anti-TNF alfa (TNF+) and 258 patients treated with DMARDs (TNF-).

Exposure	n. patients	Patient-years (×100)	MI events/100 patients/year	Heart failure/100 patients/year
TNF+	86	855.87	14.5	11
TNF-	258	3452.62	7.8	6.6

TNF- groups respectively, with a incidence rate ratio of 1:8 (Table 4).

Analyzing the rate of Framingham risk factors at baseline and at the moment of the last evaluation, a significant higher rate of hypertension was observed in both groups: from 33.7% to 55.8% in TNF+ (p: 0.005) and from 27% to 49.6% in TNF- (p: 0.0001). No difference in hypercholesterolemia, hyper-trygliceridemia, diabetes mellitus, and smoking habits was observed in two groups during follow-up.

When we analyzed patients only with MI (38 cases) compared with patients without CV events (279 cases), higher frequency of male gender (p: 0.0001), higher mean age at RA onset (p: 0.0009) and at first evaluation (p: 0.01), baseline dyslipidemia (p: 0.0002), familiar CV disease (p < 0.0001), diabetes (p < 0.0001), CAD (p: 0.03) were associated with MI at univariate analysis (Table 5).

An incidence rate of heart failure of 11% patient-year in TNF+ group and 6.6% patient-year in TNF- group was observed with an incidence rate ratio of 1.68 (Table 4).

Heart failure occurred in 14 cases on 65 CV events (21.5%): higher age at RA onset (p: 0.04), higher age at baseline (p: 0.006), anti-TNF alpha drugs (p: 0.038), dyslipidemia (p: 0.038), coronaropathy (p: 0.018), higher Framingham score (p < 0.0001), and positivity for anticardiolipin antibodies (p: 0.0013) are associated with heart failure, at univariate analysis (Table 5). Analysis of adjusted HR for all CV events, MI and heart failure did not confirm a significant association with TNF alpha drug exposure, due to wide confidence intervals (Table 6).

Discussion

In this monocentric study, we retrospectively analysed the occurrence of CV events of a cohort of RA patients with long duration of anti-TNF alpha treatment. CV events occurred in 18.9% of cases, mainly represented by MI (43%), heart failure (21.6%) and stroke (10.8%) without significant different distribution between TNF+ and TNF- cases. Patients taking TNF alpha therapy did not show higher number of Framingham risk factors or higher age, but a longer RA duration and higher disease activity at baseline comparing with patients taking DMARDs. A long duration of persistent active disease represents a surrogate marker of systemic inflammation and play a pivotal role in inducing widespread atherosclerosis [5] and CV events. Basing on these data, according to EULAR recommendations, the Framingham CV risk value should be multiplied for 1.5-times if patients showed a long disease duration [21].

Patients taking anti-TNF alpha therapy showed an incidence rate of CV events two-fold higher (2.5% patient-year) comparing with TNF- one (1.27% patient-year). In addition, the events seem to occur earlier in TNF+ group (after a mean of 8.3 years) that what found in TNF- group (mean: 13.3 years). Nevertheless, anti-TNF alpha treatment does not actually represent an

Table 5: Comparison between 38 patients with miocardial infarct (MI) and 279 patients without CV events; 14 patients with heart failure and 279 patients without CV events.

		MI (n. 38)	Without CV events (n. 279)	p	Heart failure (n. 14)	p
Demographics	F/M	8/15	224/75	0.0001	11/3	1.0
	Mean age at onset, years (SD)	55 (11)	45.7 (15.6)	0.0009[a]	54.5 (13.4)	0.04[a]
	Mean age at baseline, years (SD)	60 (9.9)	54.3 (11.9)	0.01[a]	63.3 (9.6)	0.006[a]
	Mean drug exposure duration, years (SD)	11.3 (7.3)	18.4 (8.8)	0.2[a]	11.3 (7.3)	0.48[a]
	Mean RA duration at last observation, years (SD)	13.28 (7.4)	18.4 (8.8)	0.6[a]	19.4 (7.1)	0.7[a]
	Anti-TNF alfa exposure, n. (%)	8/38 (21)	65/214 (30.3)	0.33	8/14 (57)	0.038
Comorbidities	Arterial hypertension (%)	7/32 (21.8)	41/156 (26.2)	0.66	5/11 (45.5)	0.17
	Smoking habits (%)	4/13 (30.7)	37/156 (23.7)	0.5	1/11 (9)	0.46
	Dyslipidaemia (%)	13/32 (40.6)	17/153 (11.1)	< 0.0001	5/14 (35.7)	0.038
	Familiar CV disease (%)	25/32 (78)	113/279 (40.5)	< 0.0001	9/14 (64.3)	0.09
	Diabetes (%)	8/20 (40)	7/156 (4.4)	< 0.0001	2/11 (18.2)	0.1
	Coronaropathy (%)	2/16 (12.5)	4/279 (1.4)	0.03	2/11 (18.2)	0.018
	Mean n. Framingham risk factors at the CV event (SD)	11.1 (10)	5.98 (7.2)	0.0001[b]	18.54 (14.5)	< 0.0001[b]

[a] = unpaired t test, [b] = Mann-Withney test.

Table 6: Crude and adjusted hazard ratio for all CV events, myocardial infarction (MI) and heart failure.

	Crude HR (95%CI)	Adjusted HR (95%CI)*
All events	2.44 (1.39-4.27)	1.81 (0.86-3.82)
MI	1.85 (0.78-4.39)	1.06 (0.32-3.51)
Heart failure	6.32 (2.02-19.73)	2.34 (0.54-10.14)

*adjusted for age sex, CV risk score, baseline disease activity, RF, glucocorticoids, NSAIDs.

additional risk factor for CV events: multivariate analysis showed that only higher age at RA onset, diabetes and coronary artery disease were significantly associated with CV events occurrence. In addition, Cox analysis showed that only Framingham risk score is slightly associated with CV events, while anti-TNF alpha exposure showed a wide dispersion data to draw conclusions. A wide meta-analysis confirms an overall protection of anti-TNF alpha drugs for almost all major CV events [23]: in particular, the use of anti-TNF alpha has been widely demonstrated to give a protective effect on the onset of MI [15,16,24], especially in patients with continuative use of the drugs [15]. Nevertheless, this protective effect is not significant for TIA/stroke [16] and heart failure [23]. The National British registry fails to demonstrate a global reduction of the rate of MI in patients treated with anti-TNF alpha, anyway responders to anti-TNF alpha showed a significant reduction of the incidence of MI compared with non-responders [14].

Our cohort is comparable to the others published so far for long duration of RA [15,16,24], high disease activity [14,15,24] and the rate of different CV risk factors [14-16,24]. Given these clinical similarities, the failure of demonstrating a protective effect on CV events is probably due to the small number of patients considered in our study. In fact, when we previously analyzed a smaller control group (TNF-), anti-TNF exposure showed a strict correlation with the occurrence of CV events (data not shown). TNF- group had been selected basing on patients currently followed-up. In order to by-pass this selection bias, we have increased the number of TNF- cases, randomly chosen within all patients that were followed up in same period considered for all anti-TNF+ patients analyzed. Expanding the cohort, we found that the use of anti-TNF alpha is not significantly correlated with any CV events, even if these patients are more at risk to develop a major CV event, in particular heart failure, due to their long duration of disease and traditional CV risk factors.

According to EULAR recommendations, a CV risk assessment should be performed at baseline and every year during follow-up, including arterial pressure measurement, lipid profile analysis and accurate CV patients' history [21]. Data derived from clinical charts show that a correct CV risk assessment has been done in every patient, also in RA cases onset and followed before 2000s. Anyway, the assessment of total cholesterol/HDL ratio is lacking: this data represents one of the most important predictive factor of the CV events occurrence [22], particularly in those cases with high disease activity [25].

At univariate analysis hydroxychloroquine seems to represent a protective element for the development of CV events. This immunomodulant drug is known to have a vaso-protective effect, inhibiting inflammation cascade and endothelial dysfunction process [26]. In addition, observational studies suggested favorable effects on lipid profile [27,28] and a reduction of CV events occurrence in RA patients [29]. A similar protective effect was demonstrated in Systemic Lupus Erythematosus for thromboembolic events [30].

When we analyzed only the occurrence of MI and heart failure, we found a similar distribution of MI between TNF+ and TNF- groups, while a significant higher incidence of heart failure was observed in TNF+ cases.

Diabetes and CAD represent the major risk factors for the development of MI, as in general population [31]. Higher age at RA onset, higher age at baseline and higher Framingham risk score are significantly associated with heart failure. The occurrence of heart failure has been recently reported in 24% of RA patients, independently from RA treatments: it is a predominant diastolic failure and it is associated with higher disease activity. long disease duration and left ventricular hypertrophy [32]. We previously demonstrated a higher left ventricular mass, and impaired diastolic function, as well as a higher aortic stiffness, in a small cohort of RA patients without any CV risk factors [33]. These data confirm that high and long-standing inflammatory burden of RA, even in absence of CV risk factors, could lead to a persistent endothelial activation with consequent impairment of LV diastolic function and heart failure. This high-risk magnitude is comparable to that found in type 2 diabetes [34,35]. Endothelial dysfunction and arterial stiffness are widely reported during RA [36], also in patients without CV risk factors [37,38]. The use of TNF alpha inhibitors does not seem to significantly modify the progression of carotid atherosclerosis [39] Some authors reported an improvement of endothelial function in these patients, but with transient effect [40].

During 10-years follow-up, the incidence of arterial hypertension significantly increased in both TNF+ and TNF- groups, while the occurrence of other CV risk factors was somewhat stable in both groups. This could be due a strict clinical monitoring of CV risk factors in two RA populations. These data confirm a recent paper, reporting a similar management and aggressive treatment of different CV risk factors on a wide cohort of RA and controls in 4-years follow-up [41].

This study showed some limitations. First: the relatively small number of cases, as discussed above; second: TNF+ and TNF- groups are not balanced for RA duration and disease activity at baseline, resulted in both cases higher in TNF+ patients. We tried to correct this bias, matching TNF+ and TNF- patients for disease duration before starting anti-TNF alpha or DMARDs treatment, respectively. In this sub-analysis, the CV events showed a similar incidence rate in two groups (1.27% patient-years in TNF+ vs. 1.3% patient-year in TNF-) and are associated only with higher age at baseline, by multivariate analysis.

In conclusion, a correct analysis of CV risk factors and an aggressive treatment of inflammatory burden should be performed on every patient affected by RA, given the high annual rate of major CV events during follow-up. A study of extension of atherosclerosis on vascular tree should be considered, at least in patients with highest CV risk profile.

Conflict of Interest

Authors declare no conflict of interests.

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