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Review

The effect of non-TNF-targeted biologics on vascular dysfunction in rheumatoid arthritis: A systematic literature review

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ABSTRACT

Background: Rheumatoid arthritis (RA) is burdened by a significant increase in cardiovascular disease (CVD) risk. Amongst CVD risk factors, endothelial dysfunction and arterial stiffness represent powerful predictors of atherosclerosis and cardiovascular events in the general population and in RA patients.
Methods: A systematic review of the literature was performed to identify the available data on the effect of non-TNF-targeted biologics licensed for the treatment of RA on endothelial function, arterial stiffness or subclinical atherosclerosis. MedLine (via PubMed), Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science (WOS) databases were searched using a predefined strategy to identify relevant articles.
Results: The search strategy initially retrieved 389 records. After screening titles and abstracts, a total of 362 studies were excluded. Amongst the remaining 27 studies selected for final examination, 16 articles were included in the systematic literature review. Included studies demonstrated a significant effect of abatacept, anakinra, rituximab and tocilizumab in improving endothelial dysfunction associated with RA; the effect on arterial stiffness was less consistent and deserves further investigation. No significant effect of non-TNF-targeted biologics was observed for measures of subclinical atherosclerosis.
Conclusion: Non-TNF-targeted biologics have been associated with favorable effects on endothelial dysfunction as already demonstrated for TNF inhibitors. Future studies are needed to ascertain the impact of this mediations on arterial stiffness in RA patients.

1. Introduction

Rheumatoid arthritis (RA) is characterized by an excess of cardiovascular diseases (CVD) risk [1,2], comparable in magnitude to that conferred by type 2 diabetes mellitus (T2D) [3]. This profile results from the interaction between the prejudicial effect of systemic inflammation on vascular function and an increased prevalence of “traditional” cardiovascular risk factors [4,5]. Indeed, literature evidence shows that CVD risk factors such as high blood pressure [6], T2D [7,8], insulin resistance [9,10] and dyslipidemia [11] are still underdiagnosed and undertreated in RA patients. Amongst emerging CVD risk factors, an important role is played by endothelial dysfunction, a measurable phenomenon independently predictive of cardiovascular events in the general population [12]. Indeed, the endothelium is the main regulator of vascular homoeostasis and is essential in maintaining control of arterial tone, coagulation status, and smooth muscle cells proliferation [13]. Conversely, endothelial dysfunction is a condition characterized by an imbalance between vasodilating mediators with anti-mitogenic and anti-thrombogenic activity such as nitric oxide (NO) and prostacyclin, and vasoconstricting mediators with prothrombotic, proliferative effects such as endothelin-1 (ET-1) [14,15]. Injury to the vascular endothelium is the preliminary event in most vascular disorders, leading to arterial stiffening [16], subclinical atherosclerosis and culminating in a full-blown arterial disease [17]. An impaired endothelial function has been largely demonstrated in RA patients [18] and represents a powerful contributor to the progression of atherosclerosis in this population [19].

Several techniques have been developed for the invasive and non-invasive assessment of individual aspects of vascular function in humans. Endothelial function is evaluated mainly by quantifying the vascular response to pharmacological or physical stimuli (i.e. acetylcholine, experimental ischemia). To date, flow-mediated dilatation (FMD), venous occlusion plethysmography (VOP), and laser-Doppler iontophoresis (LDI) have been largely validated in clinical studies,

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although each technique has advantages and disadvantages [15]. On the other side, the elastic properties of the arterial wall (arterial stiffness) are best evaluated using non-invasive measures such as pulse wave velocity (PWV) [20] or peripheral arterial tonometry (PAT) [21]; while the most used surrogate of subclinical atherosclerosis is the measurement of carotid artery intima-media thickness (cIMT) [22].

Inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) have a well-recognized role in RA pathogenesis [23,24]. Similarly, preclinical and clinical evidence support the role of TNF-α in atherosclerosis. Higher circulating levels of TNF-α are detectable in CVD patients and TNF-α itself is able to directly impair endothelial function by reducing NO-synthase expression and triggering NF-κB activation and reactive oxygen species accumulation in endothelial cells [25]. Anti-TNF-α therapy [26], now a cornerstone of RA treatment together with other biologic agents, has been demonstrated to improve cardiovascular outcomes and to reduce several cardiovascular risk factors [27–30], including endothelial dysfunction [31].

In the last years, the therapeutic armamentarium against RA has been enriched with the approval of additional biologic agents (abatacept, anakinra, rituximab, tocilizumab) and, more recently, small molecules (tofacitinib, baricitinib). Similarly to what already observed for TNF inhibitors (TNFi), all non-TNF-targeted biologics have been associated with some degree of reduction of the overall CVD risk in treated individuals [32]. Unfortunately, little is known about the effect of these newer medications on vascular function. Based on this background, the main aim of the present article was to review the available evidence on a potential effect on vascular physiology of non-TNF-targeted biologics approved for the treatment of RA.

2. Methods

2.1. Aim of the systematic literature review

A systematic review of the literature was performed to identify the available data on the effect on endothelial function, arterial stiffness or subclinical atherosclerosis of non-TNF-targeted biologics licensed for the treatment of RA.

2.2. Search strategy

MedLine (via PubMed), Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science (WOS) databases were searched up to August 2018. The main search in MedLine was conducted using the string *("abatacept" OR "anakinra" OR "rituximab" OR "tocilizumab") AND ("atherosclerosis"[MESH] OR "vascular stiffness"[MESH] OR "Carotid Intima-Media Thickness"[Mesh] OR "pulse wave velocity" OR "pwv" OR "endothelial function" OR "endothelial dysfunction" OR "flow mediated dila*" OR "FMD" OR "forearm blood flow" OR "FBF" OR "peripheral arterial tonometry" OR "PAT").* The main search in WOS was performed using the string #1 TOPIC: (abatacept) OR TOPIC: (anakinra) OR TOPIC: (rituximab) OR TOPIC: (tocilizumab) and #2 TOPIC: (atherosclerosis) OR TOPIC: (vascular stiffness) OR TOPIC: (intima media thickness) OR TOPIC: (pulse wave velocity) OR TOPIC: (endothelial function) OR TOPIC: (endothelial dysfunction) OR TOPIC: (flow mediated dila*) OR TOPIC: (forearm blood flow) OR TOPIC: (peripheral arterial tonometry) OR TOPIC: (IMT) OR TOPIC: (PWV) OR TOPIC: (FMD) OR TOPIC: (FBF) OR TOPIC: (PAT).

Additionally, relevant keywords were used in different combinations for free-hand search and bibliography of selected articles was reviewed in order to improve the sensitivity of the search strategy. The search was designed and performed by one author (FU).

2.3. Inclusion criteria and study selection

To be included in the final review, studies (full-text articles or conference papers) had to meet the following inclusion criteria:

1) **Study design:** randomized controlled trial (RCT), *quasi*-RCT (trials in which allocation to treatment was made by alternation, use of alternate medical records, date of birth or other expected methods), prospective (before-after) cohort study;
2) **Population:** studies involving human subjects;
3) **Intervention:** treatment with abatacept or anakinra or rituximab or tocilizumab;
4) **Outcome:** evaluation of the effect of treatment on measures of endothelial function, vascular stiffness or subclinical atherosclerosis.

In addition, we applied the following exclusion criteria: **a)** studies published in language different from English; **b)** studies (both as a full text or congress abstract) not reporting pre-post values or at least pre-post comparison *p* values.

2.4. Study identification and data extraction

Two reviewers (FU and PR) independently screened titles and abstracts of retrieved records for inclusion in the systematic review. After screening phase, the same two reviewers independently evaluated the remaining articles to determine eligibility according to the inclusion and exclusion criteria. Disagreements amongst the reviewers were resolved by discussion with a third senior reviewer (RDG) until reaching a final consensus. All the data related to the evaluation of the effect of treatment on measures of endothelial function, vascular stiffness or subclinical atherosclerosis were recorded. A detailed flowchart of the study selection process is depicted in Fig. 1.

2.5. Reporting method

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for preparing our manuscript [http://www.prisma-statement.org/] (Supplementary Table 2).

3. Results

3.1. Search results

The search strategy initially retrieved 389 records. No additional citations were added by hand-search of relevant articles bibliography. After screening titles and abstracts, a total of 362 studies were excluded because of duplicates, non-English language, review articles, preclinical studies or clinical studies dealing with the wrong population, intervention or outcome. Amongst the remaining 27 studies selected for final examination, 16 articles were included in the systematic literature review. The causes of exclusion at each step are summarized in Fig. 1. The descriptive features of selected articles are outlined in Table 1 whereas the main results are summarized in Table 2.

All the selected studies evaluated one or more aspects of vascular functioning using surrogate measures of endothelial dysfunction (flow-mediated dilatation, FMD; coronary flow reserve, CFR; laser-Doppler flowmetry, LDF), arterial stiffness (pulse wave velocity, PWV; augmentation index, AIx; cardio-ankle vascular index, CAVI) and preclinical atherosclerosis (common carotid intima-media thickness, cIMT). A synthetic description of the techniques is provided in supplementary Table 1.

3.2. Abatacept

The systematic literature review retrieved 2 papers about abatacept, a recombinant fusion protein selectively modulating the CD80/86-CD28 co-stimulatory signal required for T-cell activation.

In a cohort study by Mathieu et al. [33], RA patients refractory to at least two TNFi or presenting contraindications were recruited. The authors investigated the effects of treatment with abatacept on aortic stiffness measured by PWV on 21 patients (17 females). A significant

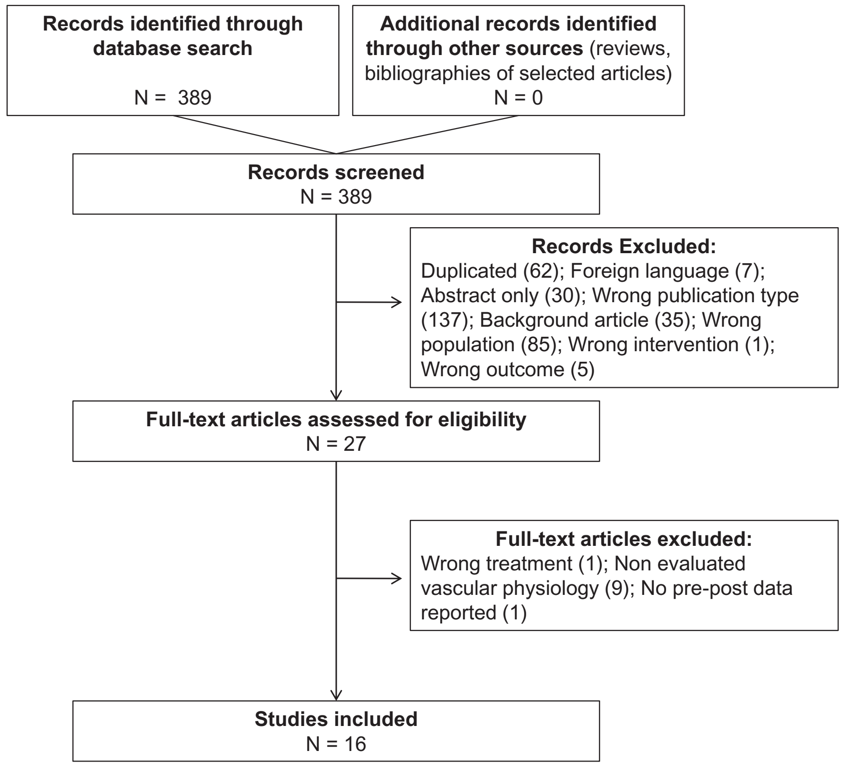

Fig. 1. Study selection flow-chart. The process of studies selection is synthetized. Causes of exclusion at each step are reported (in parentheses the number of studies excluded for each individual cause).

improvement of PWV was observed following 6 months of treatment with abatacept (8.5 ± 3.9 vs 9.8 ± 2.9 m/s, $p = 0.02$) [33].

In another observational longitudinal study, Provan et al. [34] assessed PWV on RA patients at baseline and after 3, 6 and 12 months of treatment with abatacept, rituximab or tocilizumab. Of the 36 patients included, 5 received abatacept, 24 rituximab and 7 tocilizumab. Due to low number of patients in abatacept and tocilizumab groups, only data from the rituximab patients were analyzed over the 12-month period. However, when looking at the 6 abatacept-treated patients, no significant within group change in PWV was reported after 3 months (0.3 ± 0.6 m/s, $p = 0.23$) when compared with baseline values (6.8 ± 1.2 m/s) [34].

3.3. Anakinra

The systematic literature review retrieved 2 papers from the same group about anakinra, a recombinant human IL-1 receptor antagonist.

The first paper by Ikonomidis et al. [35] assessed both the “acute” and “chronic” effects of anakinra administration on vascular function assessed using both FMD and PWV. To evaluate the “acute” effects, the Authors performed a double-blind trial, in which patients with RA were randomized to receive a single subcutaneous injection of anakinra or placebo and, after 48 h, the alternative treatment. FMD and PWV were assessed at baseline, before the administration of anakinra, and 3 h after the injection. Analyzing the results of the first phase which enrolled 23 patients (17 females), FMD increased after treatment with anakinra (5.3% ± 3.0 vs 9.7% ± 3.3, $p < 0.001$) whereas it decreased after placebo (5.3% ± 3.0 vs 4.8% ± 2.7, $p = 0.9$). Conversely, PWV did not change nor after anakinra (9.4 ± 2.8 vs 9.5 ± 2.7 m/s, $p = 0.7$) or placebo (9.4 ± 2.8 vs 9.3 ± 2.4 m/s, $p = 0.9$). In the second phase of the study, the “chronic” effects of anakinra on vascular function were assessed in a 30–day non-randomized trial including 23 patients treated with anakinra and 19 patients treated with prednisolone. In anakinra-treated patients, FMD increased (5.3% ± 3.0 vs 10.5% ± 4.1, $p < 0.001$) whereas no improvement was observed in prednisone-treated patients (5.0% ± 1.9 vs 4.3% ± 1.6, $p = 0.25$). Conversely, PWV did not change nor after anakinra (9.4 ± 2.8 vs 9.5 ± 2.7 m/s, $p = 0.7$) or prednisone (9.8 ± 1.8 vs 9.6 ± 2.6 m/s, $p = 0.7$) [35].

In another double-blind crossover trial [36], the same Authors investigated the effects of anakinra on coronary artery endothelial function. Eighty RA patients treated with synthetic disease-modifying antirheumatic drugs (sDMARDs) were randomized to a single injection of anakinra or placebo and after 48 h of the alternative treatment; FMD and coronary flow reserve (CFR) were performed at baseline and 3 h after treatment. After treatment with anakinra, the Authors reported a significant improvement in FMD (4.2% ± 1.5 vs 9.7% ± 2.4, $p < 0.05$) and CFR (2.1 ± 0.6 vs 2.9 ± 0.8, $p < 0.05$) [36].

3.4. Rituximab

The vascular effects of rituximab, a chimeric monoclonal antibody against CD20, were investigated in different articles identified through the search strategy.

Gonzalez-Juanatey et al. [37] investigated the effect of rituximab on endothelial function in six patients with RA previously treated with synthetic DMARDs and TNFi. An early improvement of FMD was observed after 2 weeks (3.35% ± 1.58 vs 7.02% ± 2.31, $p = 0.03$); the result was maintained in all treated patients (3.35% ± 1.58 vs 7.66% ± 1.73, $p = 0.03$) after 6 months [37].

In a study by Kerekes et al. [38], the effects of rituximab on FMD and common carotid intima–medial thickness (cIMT) were investigated in 5 RA patients treated with rituximab, before the treatment and at weeks 2, 6, and 16. Treatment with rituximab significantly improved FMD at week 16 (3.92% ± 1.47 vs 7.24% ± 3.35, $p = 0.02$). A progressive increase of this parameter was observed during the follow-up, with an improvement in FMD of 30%, 22%, and 81% at weeks 2, 6, and 16, respectively. Conversely, although a trend toward reduction was observed during the follow-up, no significant changes of cIMT was

Table 1
Descriptive features of the selected studies.

First author, year	Design	Medication	n° patients (males)	Controls, treatment (n°)	Age, years	Disease duration	Baseline DAS28	Previous Medications	Outcome	Follow-up
Gonzalez-Juanatey [37]	Observational	RTX	6 (1)	–	65 (55 to 79)	16 (3 to 34) years	5.17 ± 0.62	sDMARDs, TNFi	FMD	6 months
Ikonomidis [35]	Observational	ANA	23 (6)	Prednisolone (19)	57 ± 17	11 (1–27) years	5.1 ± 0.9	sDMARDs	FMD PWv	1 month 1 month
Kerekes [38]	Observational	RTX	5 (0)	–	41.6 (29 to 56)	5.8 (1 to 9) years		sDMARDs, TNFi	FMD cIMT	16 weeks 16 weeks
Kume [44]	Observational	TCZ	21(3)	ETN (21), ADA (21)	62 ± 16	10 ± 6 months	5.22 ± 1.6	None	CAVI Aix@75 cIMT	24 weeks 24 weeks 24 weeks
Protogerou [45]	Observational	TCZ	11 (0)	–	44.2 ± 9.8	–	5.5 ± 1.2	–	FMD PWv	6 months 6 months
Mathieu [39]	Observational	RTX	33 (4)	–	60.9 ± 12	17.6 ± 8.6 years	5.7 ± 1.1	sDMARDs, TNFi	AIx PWv	12 months 12 months
Benucci [41]	Observational	RTX	38 (5)	–	66.4 ± 10.6	5.8 (1 to 9) years	5.84 ± 0.8	sDMARDs, TNFi	FMD cIMT	24 weeks 24 weeks
Mathieu [33]	Observational	ABA	21 (4)	–	65.2 ± 13.7	21.5 ± 10 years	5.1 ± 1.1	sDMARDs, TNFis	PWv	6 months
McInnes [46]	Randomized controlled trial	TCZ	65 (8)	PBO (60)	57.0 (49.0–62.0)	6.8 (2.4–9.9) years	6.6 (5.8–7.3)	sDMARDs, TNFis	PWv	24 weeks
Hsue [40]	Observational	RTX	20 (1)	–	53 (46–62)	12 (6.5 to 14.75) years	6.6 (6.1–7.1)	sDMARDs, sTNFis	FMD cIMT	24 weeks 24 weeks
Ikonomidis [36]	Randomized controlled trial (cross-over)	ANA	60 (20 with CAD)	PBO (60)	59.5 ± 18	12 (5–23.5) years	4.7 ± 1	sDMARDs	FMD CFR	3 hours 3 hours
Meshcherina [42]	Observational	RTX	22	IFX (18)	40.1 (36.8–47.3)	15.1 (9.3–21.8) months	5.7 (4.44–6.70)	sDMARDs	Angioscan occlusion index	12 months
Provan [34]	Observational	ABA	5		53.9 (41 to 67)	–	5.1 ± 0.6	–	PWv	3 months
		RTX	24		56.9 (25 to 72)	–	4.7 ± 1.3	–	PWv	3 months
		TCZ	7		52.3 (36 to 59)	–	5.3 ± 1.2	–	PWv	3 months
Novikova [43]	Observational	RTX	55 (0)	–	50.4 ± 1.7	98 ± 9 months	6.2 ± 0.1	sDMARDs, TNFis	DVP stiffness index cIMT	6 months 6 months
Ruiz-Limon [47]	Observational	TCZ	20 (4)	–	47.8 ± 2.30	7.6 ± 1.76 years	4.25 ± 0.18	sDMARDs	LD peak flow	6 months
Bacchiega [48]	Prospective Community-Based Clinical Study	TCZ	17 (2)	MTX (6), LEF (8), ETN (7), ADA (2)	51.7 [44.52–58.90]	12.1 [8.39–15.84] years	5.87 [5.29–6.44]	None	FMD	16 weeks

Data are presented as follows: x ± y, mean ± SD; x (y to z), mean (range); x (y − z), median (IQR); x [y − z], mean (95% CI of the mean).
Abbreviations: RTX: rituximab; ANA: anakinra; TCZ: tocilizumab; ABA: abatacept; ETN: etanercept; ADA: adalimumab; PBO: placebo; IFX: infliximab; MTX: methotrexate; LEF: leflunomide; sDMARDs: synthetic disease-modifying antirheumatic drug; TNFi: tumor necrosis factor inhibitor; FMD: flow mediated dilatation; PWv: pulse wave velocity; CFR: coronary flow reserve; cIMT: carotid intima media tickess; CAVI: Cardio-ankle vascular index; Aix: Augmentation index; DVP: digital volume pulse; LD laser Doppler.

Table 2
Main findings of the selected studies.

First author, year	Design	Medication	Outcome	Follow-up	Outcome Pre-treatment	Outcome Post-treatment	Significance level	Main Findings
Gonzalez-Juanatey [37	Observational	RTX	FMD	6 months	3.35 ± 1.58	7.66 ± 1.73	0.03	Improvement in FMD
Ikonomidis [35]	Observational	ANA	FMD	1 month	5.3 ± 3.0	10.5 ± 4.1	< 0.001	Improvement in FMD
			PWv	1 month	9.4 ± 2.8	9.5 ± 2.9	0.7	No significant change in PWv
Kerekes [38]	Observational	RTX	FMD	16 weeks	3.92 ± 1.47	7.24 ± 3.35	0.02	Improvement in FMD
			cIMT	16 weeks	0.64 ± 0.11	0.63 ± 0.07	0.39	No significant change in cIMT
Kume [44]	Observational	TCZ	CAVI	24 weeks	10.72 ± 1.22	Δ = 0.85 ± 0.15	0.02	Improvement in CAVI
			Aix@75	24 weeks	38.1 ± 5.4	Δ = 3.59 ± 0.33	0.03	Improvement in Aix@75
			cIMT	24 weeks	1.1 ± 0.1	Δ = 0.00 ± 0.13	> 0.05	No significant change in cIMT
Protogerou [45]	Observational	TCZ	FMD	6 months	3.3 ± 0.8	5.2 ± 1.9	0.021	Improvement in FMD
			PWv	6 months	8.2 ± 1.2	7.0 ± 1.0	0.009	Improvement in PWv
Mathieu [39]	Observational	RTX	AIx	12 months	30.4 ± 8.2	29.4 ± 6.7	0.22	No significant change in Aix
			PWv	12 months	8.1 ± 3.1	8.0 ± 2.7	0.92	No significant change in PWv
Benucci [41]	Observational	RTX	FMD	24 weeks	5.24 ± 1.12	5.43 ± 1.16	0.03	Improvement in FMD
			cIMT	24 weeks	0.69 ± 0.16	0.67 ± 0.12	0.25	No significant change in cIMT
Mathieu [33]	Observational	ABA	PWv	6 months	8.5 ± 3.9	9.8 ± 2.9	0.02	Improvement in PWv
McInnes [46]	Randomized controlled trial	TCZ	PWv	24 weeks	9.0 ± 2.0	9.0 ± 2.3	–	No significant change in PWv
Hsue [40]	Observational	RTX	FMD	24 weeks	3.9 (3.4–5.8)	4.3 (3.3–6.1)	0.25	Improvement in FMD
			cIMT	24 weeks	0.97 ± 0.06	0.98 ± 0.06	0.89	No significant change in cIMT
Ikonomidis [36]	Randomized controlled trial (cross-over)	ANA	FMD	3 hours	4.2 ± 1.5	9.7 ± 2.4	< 0.05	Improvement in FMD
			CFR	3 hours	2.1 ± 0.6	2.9 ± 0.8	< 0.05	Improvement in CFR
Meshcherina [42]	Observational	RTX	Angioscan occlusion index	12 months	Not reported	+48.8%	0.001	Improvement in Angioscan occlusion index
Provan [34]	Observational	ABA	PWv	3 months	6.8 ± 1.2	Δ = 0.3 ± 0.6	0.23	No significant change in PWv
		TCZ	PWv	3 months	7.7 ± 1.4	Δ = 0.1 ± 0.8	0.69	No significant change in PWv
		RTX	PWv	3 months	7.8 ± 1.6	Δ = −0.9 ± 1.0	0.03	Improvement in PWv
Novikova [43]	Observational	RTX	DVP stiffness index	6 months	14.7 ± 0.9	9.9 ± 0.9	< 0.05	Improvement in DVP stiffness index
			cIMT	6 months	0.77 ± 0.03	0.69 ± 0.02	< 0.05	Improvement in cIMT
Ruiz-Limon [47]	Observational	TCZ	LD peak flow	6 months	71.23 ± 6.08	87.17 ± 10.10	0.01	Improvement in LD peak flow
Bacchiega [48]	Prospective Community-Based Clinical Study	TCZ	FMD	16 weeks	3.43 [1.28–5.58]	5.96 [3.95–7.97]	0.03	Improvement in FMD

Data are presented as follows: x ± y, mean ± SD; x (y to z), mean (range); x (y − z), median (IQR); x [y − z], mean (95% CI of the mean).
Abbreviations: RTX: rituximab; ANA: anakinra; TCZ: tocilizumab; ABA: abatacept; FMD: flow mediated dilatation; PWv: pulse wave velocity; CFR: coronary flow reserve; cIMT: carotid intima media tickess; CAVI: Cardio-ankle vascular index; Aix: Augmentation index; DVP: digital volume pulse; LD laser Doppler.

reported (0.64 ± 0.11 vs 0.63 ± 0.07 mm, p = 0.39) [38].

Mathieu et al. [39] investigated arterial stiffness, assessed by PWV and AIx in 33 RA patients undergoing treatment with rituximab, after 6 and 12 months. After treatment with rituximab, no change was reported in PWV neither after 6 or 12 months (baseline: 8.1 ± 3.1, 6 months: 8.1 ± 2.8, 12 months 8.0 ± 2.7 m/s, p = 0.924). Similarly, no change in AIx was reported (baseline: 30.4% ± 8.2, 6 months: 28.6% ± 7.6, 12 months: 29.4 ± 6.7, p = 0.216) [39].

Hsue et al. [40] performed an observational study to investigate the effects of treatment with rituximab on FMD and cIMT in 20 RA patients previously treated with sDMARDs and TNFi. After treatment with rituximab, FMD improved at week 12 (4.5% ± 0.4 vs 6.4% ± 0.6, p < 0.0001), followed by a decline at week 24 (4.5% ± 0.4 vs 5.2% ± 0.6, p = 0.25). In these cohort, the Authors did not observe an improvement of mean cIMT from baseline to week 24 (0.97 ± 0.06 vs 0.98 ± 0.06 mm, p = 0.89) [40].

In an observational study, Benucci et al. [41] assessed FMD and cIMT in 38 RA previously treated with sDMARDs and TNFi, before and after treatment with rituximab. The results showed an improvement of FMD (5.24% ± 1.12 vs 5.43 ± 1.16, p = 0.03) and a non-significant change in cIMT (0.69 ± 0.16 vs 0.67 ± 0.12 mm, p = 0.25) after 24 months of follow-up [41].

In the observational study by Meshcherina et al. [42], vasomotor endothelial function was evaluated by a proprietary photoplethysmography device (AngioScan-01, AngioScan-Electronics, Russia), before and after 12 months of treatment with rituximab in 77 RA patients of which 39 treated with rituximab. The authors analyzed separately seropositive and seronegative patients: the first group consisted of 22 patients with median age of 40.1 years (36.8–47.3), the second group comprised 17 patients with median age of 34.5 years (28.1–48.5). No significant baseline differences were reported between these groups. Furthermore, the Authors also assessed 46 healthy controls with median age of 38.6 years (32.1–47.8). RA patients showed signs of endothelial dysfunction in micro- and macro-circulatory vasculature, including the decrease of occlusion index in amplitude and the value of phase shift between the channels after a reactive hyperemia test. After 12 months, both groups of patients showed an increase of occlusion index in amplitude up to the control values; as compared with the baseline values, the phase shift between the channels increased on average by 1.6 times (p = 0.0024) during treatment with rituximab. The occlusion index in amplitude increased by 23.5% by 48.8% (p = 0.001) during rituximab treatment [42].

In the previously mentioned study by Provan et al. [34] the Authors assessed PWV in RA patients treated with different biologics, including 24 individuals undergoing treatment with rituximab. After 12 months of treatment, a significant within group reduction on PWV was reported in rituximab-treated patients [estimated marginal means 7.7 (7.2–8.2) vs 7.3 (6.8–7.9) m/s, p = 0.04] [34].

Novikova et al. [43] assessed the effects of rituximab on arterial stiffness and cIMT in RA by a 6-month observational study. The study assessed 55 female patients previously treated with sDMARDs and TNFi. Based on the European League Against Rheumatism (EULAR) criteria, patients were categorized into two groups: 1) moderate/good response to rituximab (41 patients, 75%), no response to rituximab (14 patients, 25%). Treatment with rituximab led to the improvement of elastic properties of the arterial walls in group 1 due to the decreased stiffness in major arteries (SI–decreased by 57%) and arterioles (RI-–decreased by 24%) and the rate of "very stiff" arteries reduced 3.5 times in group 1. The Authors further reported a 9% decrease of cIMT in this group after 6 months. On the contrary, in group 2, no significant changes were observed in any of the aforementioned vascular indexes [43].

3.5. Tocilizumab

The effects of treatment with tocilizumab, an anti-IL-6 receptor antibody, on vascular function were investigated in 6 works retrieved by the systematic literature review.

Kume et al. [44] assessed the effects of monotherapy with tocilizumab and with TNFi on arterial stiffness in 64 RA (22 treated with tocilizumab) in an open-label, 6-month, randomized controlled trial. The arterial stiffness was evaluated by using both cardio-ankle vascular index (CAVI) and aortic augmentation index normalized to a fixed heart rate of 75 bpm (AIx@75). The Authors also investigated cIMT and the presence of carotid artery plaques. In tocilizumab-treated patients, a significant improvement in CAVI was reported after 6 months (0.85 ± 0.15 m/s, p = 0.02) when compared with baseline values (10.72 ± 1.22 m/s). The Authors also observed a significant reduction of AIx@75 after 6 months (3.59% ± 0.33%, p = 0.03) when compared with baseline values (38.1% ± 5.4). On the other hand, no change was observed regarding cIMT and carotid artery plaques. Similar results were also observed after treatment with TNFi, without any significant difference when comparing the different treatment arms.

In a 6-month non-randomized prospective pilot study, Protogerou et al. [45] investigated the possible vascular effects of treatment with tocilizumab by analyzing FMD and PWV. The study assessed 16 female patients, and showed a significant increase in FMD after 6 months (3.3% ± 0.8 vs 5.2% ± 1.9, p = 0.003), whereas PWV significantly decreased (8.2 ± 1.2 vs 7.0 ± 1.0 m/s, p < 0.001) [45].

In a randomized, multicenter, two-part, phase III trial (24-week double-blind, 80-week open-label), McInnes et al. [46] evaluated vascular function by PWV in RA patients before and after treatment with tocilizumab. In this study, 69 individuals were randomized to receive tocilizumab and 63 to receive placebo. PWV decreases were greater with placebo than tocilizumab at 12 weeks (adjusted mean difference 0.79 m/s, p = 0.0067). However, this group difference was not sustained to week 24 (−0.47 vs −0.17 m/s, adjusted mean difference 0.30 m/s, p = 0.30) [46].

In the previously mentioned study by Provan et al. [46], 7 patients underwent treatment with tocilizumab. After 3 months of treatment, no significant within group change in PWV was reported (−0.9 ± 1.0 m/s, p = 0.03) when compared with baseline values (7.8 ± 1.6 m/s).

Ruiz-Limon et al. [47] assessed microvascular function by laser Doppler flowmetry in 20 RA patients, before and after treatment with tocilizumab in a 6-month observational single-arm study. After 6 months of treatment with tocilizumab, endothelial function (evaluated by Laser Doppler measurement of post-ischemic reactive hyperemia) significantly improved. The Authors reported an improvement of the highest perfusion value after the occlusion was released (peak flow 71.23 ± 6.06 vs 87.17 ± 10.10, p = 0.010) as well as an improvement of hyperemic area (2314.03 ± 300.73 vs 3846.54 ± 575.64, p = 0.041) [47].

Bacchiega et al. [48] performed a prospective community-based clinical study to investigate the effects of different treatments on FMD in 60 RA patients, of which 17 were selected to be treated with tocilizumab. An improvement in FMD was observed after 16 weeks of treatment with tocilizumab [3.43% (1.28–5.58) vs 5.96% (3.95–7.97), p = 0.03] [48].

4. Discussion

Endothelial function and elastic properties are interrelated aspects of normal arterial functioning; on the other side, their impairment (endothelial dysfunction and arterial stiffening, respectively) represents an early event in the natural history of atherosclerosis [49]. Both phenomena can be detected using non-invasive techniques several years before structural changes of the vessel wall – even preclinical such as increased cIMT – become apparent on ultrasound. Furthermore, endothelial dysfunction and arterial stiffness are mainly "functional" abnormalities that can be reverted, at least partially, by pharmacological intervention with hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or angiotensin converting enzyme inhibitors

(ACEi) [50]. For these reasons, early vascular dysfunction represents an attractive additional target in a comprehensive RA treatment plan, aimed at reducing RA-associated CVD. In this context, TNFi have been already demonstrated to improve endothelial function in RA patients [31].

The results of our systematic literature review show that also non-TNF-targeted biologics may ameliorate vascular dysfunction in patients with RA. Although with a different degree and strength of evidence, abatacept, anakinra, rituximab and tocilizumab have been all associated with an improvement of vascular endothelium-dependent vasodilatation and/or arterial stiffness in individual studies. Conversely, our systematic review failed to demonstrate any significant improvement of established structural abnormalities associated with subclinical atherosclerosis (e.g. cIMT) that, however, represent a later stage in the continuum of atherogenesis.

In RA, the inflammatory process leads to an impairment of endothelial function as a consequence of an increased nitro-oxidative stress and release of vasoconstrictive mediators, suggesting a potential role of immunosuppressive drugs in restoring the physiological functioning [51–53]. On this basis, many of the included studies have used FMD, a surrogate marker of endothelium-dependent vasodilatation, to evaluate the vascular effects of individual therapeutic agents. Interestingly, non-TNF-targeted biologics improved FMD, confirming that antagonizing the inflammatory process could have a beneficial effect on endothelial dysfunction independently on the immunological mechanism exploited, contributing to the reduce the risk of developing CVD [54]. In fact, it has been reported that early endothelial dysfunction, measured by FMD, precedes the clinical atherosclerosis with a more marked dysfunction associated with a more accelerated atherosclerotic process during the disease [55–57].

Furthermore, our systematic review suggests a potential role of non-TNF-targeted biologics on arterial stiffness. Compared with endothelial function, however, the effect on arterial stiffness was less consistent across studies reflecting an intrinsic complexity in assessing the elastic properties of the arterial wall and a marked heterogeneity between evaluated populations. Despite these limitations, abnormal stiffening of the arterial wall evaluated by means of PWV represents a well-established independent predictor of CVD in the general population [58,59] and also in RA patients, where it has been shown to predict CVD with a hazard ratio of 1.85 per unit (m/s) of increase in PWV [60]. If further confirmed in other studies, the improvement of PWV could be another possible explanation of the reduction in the development of CVD [58,59].

In our systematic review, we also investigated the effects of non-TNF-targeted biologics on measures of subclinical atherosclerosis. The ultrastructure of large arteries, such as carotids, can be easily evaluated using ultrasonography with cIMT being considered the most reliable marker of subclinical atherosclerosis, exhibiting a strong correlation with the presence of atherosclerosis in other districts and a good predictive value for incident CVD [61,62]. The usefulness of cIMT in CVD risk assessment has been consistently confirmed in RA patients [63]. Despite their vasoprotective role above mentioned, the results of our systematic review showed no or little effect of non-TNF-targeted biologics on cIMT. However, cIMT expresses the hypertrophy of intimal or medial layers (or both) and it is considered a fixed structural alteration of the arterial wall, in which non-inflammatory mechanisms play a pivotal role [64,65]. Given that, it is somewhat expected that the administration of immunomodulating agents may not be sufficient to induce regression of such an anatomical abnormality. However, it should also be noted that the short follow-up of the included studies could not be sufficient to fully disclose a slower effect of such medications [64,65] and future studies with a longer follow-up are eagerly awaited to clarify this issue.

Globally taken, the results of our systematic literature review support the hypothesis that non-TNF-targeted biologics may provide similar benefits to those observed with TNFi on cardiovascular dysfunction [31] as already proposed for RA-associated metabolic derangement [66] and suggest that the optimal control of systemic inflammation is an efficacious strategy for modifying CVD burden in its preclinical phases thus improving the long-term outcome of these patients.

Despite providing a comprehensive synthesis of the current available literature, our study has major limitations and all the results should be cautiously generalized. The main limitation of our systematic literature review is related to the poor methodological quality of most of the included studies. In fact, most studies were not RCTs, making comparison difficult. In addition, the results of individual studies are potentially influenced by the difficulties in standardization of the reported techniques, limiting the assessment of endothelial dysfunction in estimating CVD in real life clinical settings [67]. However, it must be pointed out that only non-invasive techniques could be routinely used due to the risk of complications and costs of the invasive techniques. On these bases, future studies are needed to develop new diagnostic non-invasive techniques to easily and cost-effectively identify early atherosclerosis in RA patients [68,69].

5. Conclusions

In conclusion, the results of our systematic literature review suggest that the optimal control of systemic inflammation with non-TNF targeted biologics may represent an efficacious strategy for improving endothelial dysfunction associated with RA and thus contributing to improve the long-term outcome of these patients.

Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autrev.2019.03.008.

References

[1] Avina-Zubieta JA, Thomas J, Sadatsafavi M, Lehman AJ, Lacaille D. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 2012;71(9):1524–9.

[2] Lee KS, Kronbichler A, Eisenhut M, Lee KH, Shin JI. Cardiovascular involvement in systemic rheumatic diseases: an integrated view for the treating physicians. Autoimmun Rev 2018;17(3):201–14.

[3] Lindhardsen J, Ahlehoff O, Gislason GH, Madsen OR, Olesen JB, Torp-Pedersen C, et al. The risk of myocardial infarction in rheumatoid arthritis and diabetes mellitus: a Danish nationwide cohort study. Ann Rheum Dis 2011;70(6):929–34.

[4] Innala L, Moller B, Ljung L, Magnusson S, Smedby T, Sodergren A, et al. Cardiovascular events in early RA are a result of inflammatory burden and traditional risk factors: a five year prospective study. Arthritis Res Ther 2011;13(4):R131.

[5] Giacomelli R, Afeltra A, Alunno A, Bartoloni-Bocci E, Berardicurti O, Bombardieri M, et al. Guidelines for biomarkers in autoimmune rheumatic diseases - evidence based analysis. Autoimmun Rev 2019;18(1):93–106.

[6] van Breukelen-van der Stoep DF, van Zeben D, Klop B, van de Geijn GJ, Janssen HJ, van der Meulen N, et al. Marked underdiagnosis and undertreatment of hypertension and hypercholesterolaemia in rheumatoid arthritis. Rheumatology 2016;55(7):1210–6.

[7] Ursini F, Russo E, D'Angelo S, Arturi F, Hribal ML, D'Antona L, et al. Prevalence of undiagnosed diabetes in rheumatoid arthritis: an OGTT study. Medicine 2016;95(7):e2552.

[8] Ruscitti P, Ursini F, Cipriani P, Liakouli V, Carubbi F, Berardicurti O, et al. Poor clinical response in rheumatoid arthritis is the main risk factor for diabetes development in the short-term: a 1-year, single-centre, longitudinal study. PloS one 2017;12(7):e0181203.

[9] Ursini F, Grembiale A, Naty S, Grembiale RD. Serum complement C3 correlates with insulin resistance in never treated psoriatic arthritis patients. Clin Rheumatol 2014;33(12):1759–64.

[10] Ursini F, D'Angelo S, Russo E, Arturi F, D'Antona L, Bruno C, et al. Serum complement C3 strongly correlates with whole-body insulin sensitivity in rheumatoid arthritis. Clin Exp Rheumatol 2017;35(1):18–23.

[11] An J, Cheetham TC, Reynolds K, Alemao E, Kawabata H, Liao KP, et al. Traditional cardiovascular disease risk factor management in rheumatoid arthritis compared to

matched nonrheumatoid arthritis in a US managed care setting. Arthritis Care Res 2016;68(5):629–37.
[12] Matsuzawa Y, Kwon TG, Lennon RJ, Lerman LO, Lerman A. Prognostic value of flow-mediated vasodilation in brachial artery and fingertip artery for cardiovascular events: a systematic review and meta-analysis. J Am Heart Assoc 2015;4(11).
[13] Vita JA. Endothelial function. Circulation 2011;124(25):e906–12.
[14] Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. Circulation 2007;115(10):1285–95.
[15] Sitia S, Tomasoni L, Atzeni F, Ambrosio G, Cordiano C, Catapano A, et al. From endothelial dysfunction to atherosclerosis. Autoimmun Rev 2010;9(12):830–4.
[16] Lyle AN, Raaz U. Killing me unsoftly: causes and mechanisms of arterial stiffness. Arterioscler Thromb Vasc Biol 2017;37(2):e1–11.
[17] Gimbrone Jr. MA, Topper JN, Nagel T, Anderson KR, Garcia-Cardena G. Endothelial dysfunction, hemodynamic forces, and atherogenesis. Ann N Y Acad Sci 2000;902:230–9. (discussion 9-40).
[18] Di Minno MN, Ambrosino P, Lupoli R, Di Minno A, Tasso M, Peluso R, et al. Clinical assessment of endothelial function in patients with rheumatoid arthritis: a meta-analysis of literature studies. Eur J Intern Med 2015;26(10):835–42.
[19] Ikdahl E, Hisdal J, Rollefstad S, Olsen IC, Kvien TK, Pedersen TR, et al. Rosuvastatin improves endothelial function in patients with inflammatory joint diseases, longitudinal associations with atherosclerosis and arteriosclerosis: results from the RORA-AS statin intervention study. Arthritis Res Ther 2015;17:279.
[20] Wang X, Keith Jr. JC, Struthers AD, Feuerstein GZ. Assessment of arterial stiffness, a translational medicine biomarker system for evaluation of vascular risk. Cardiovasc Ther 2008;26(3):214–23.
[21] Patvardhan EA, Heffernan KS, Ruan JM, Soffler MI, Karas RH, Kuvin JT. Assessment of vascular endothelial function with peripheral arterial tonometry: information at your fingertips? Cardiol Rev 2010;18(1):20–8.
[22] Hurst RT, Ng DW, Kendall C, Khandheria B. Clinical use of carotid intima-media thickness: review of the literature. J Am Soc Echocardiogr 2007;20(7):907–14.
[23] McGonagle D, Watad A, Savic S. Mechanistic immunological based classification of rheumatoid arthritis. Autoimmun Rev 2018;17(11):1115–23.
[24] Escarcega RO, Lipinski MJ, Garcia-Carrasco M, Mendoza-Pinto C, Galvez-Romero JL, Cervera R. Inflammation and atherosclerosis: cardiovascular evaluation in patients with autoimmune diseases. Autoimmun Rev 2018;17(7):703–8.
[25] Libby P. Inflammation in atherosclerosis. Nature. 2002;420(6917):868–74.
[26] Cacciapaglia F, Navarini L, Menna P, Salvatorelli E, Minotti G, Afeltra A. Cardiovascular safety of anti-TNF-alpha therapies: facts and unsettled issues. Autoimmun Rev 2011;10(10):631–5.
[27] Roubille C, Richer V, Starnino T, McCourt C, McFarlane A, Fleming P, et al. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. Ann Rheum Dis 2015;74(3):480–9.
[28] Barnabe C, Martin BJ, Ghali WA. Systematic review and meta-analysis: anti-tumor necrosis factor alpha therapy and cardiovascular events in rheumatoid arthritis. Arthritis Care Res 2011;63(4):522–9.
[29] Tam LS, Kitas GD, Gonzalez-Gay MA. Can suppression of inflammation by anti-TNF prevent progression of subclinical atherosclerosis in inflammatory arthritis? Rheumatology. 2014;53(6):1108–19.
[30] Leporini C, Russo E, D'Angelo S, Arturi F, Tripepi G, Peluso R, et al. Insulin-sensiting effects of tumor necrosis factor alpha inhibitors in rheumatoid arthritis: a systematic review and meta-analysis. Rev Recent Clin Trials 2018;13(3):184–91.
[31] Ursini F, Leporini C, Bene F, D'Angelo S, Mauro D, Russo E, et al. Anti-TNF-alpha agents and endothelial function in rheumatoid arthritis: a systematic review and meta-analysis. Sci Rep 2017;7(1):5346.
[32] Kang EH, Jin Y, Brill G, Lewey J, Patorno E, Desai RJ, et al. Comparative cardiovascular risk of abatacept and tumor necrosis factor inhibitors in patients with rheumatoid arthritis with and without diabetes mellitus: a multidatabase cohort study. J Am Heart Assoc 2018;7(3).
[33] Mathieu S, Couderc M, Glace B, Pereira B, Tournadre A, Dubost JJ, et al. Effects of 6 months of abatacept treatment on aortic stiffness in patients with rheumatoid arthritis. Biologics 2013;7:259–64.
[34] Provan SA, Berg IJ, Hammer HB, Mathiessen A, Kvien TK, Semb AG. The impact of newer biological disease modifying anti-rheumatic drugs on cardiovascular risk factors: a 12-month longitudinal study in rheumatoid arthritis patients treated with rituximab, abatacept and tociliziumab. PloS one 2015;10(6):e0130709.
[35] Ikonomidis I, Lekakis JP, Nikolaou M, Paraskevaidis I, Andreadou I, Kaplanoglou T, et al. Inhibition of interleukin-1 by anakinra improves vascular and left ventricular function in patients with rheumatoid arthritis. Circulation. 2008;117(20):2662–9.
[36] Ikonomidis I, Tzortzis S, Andreadou I, Paraskevaidis I, Katseli C, Katsimbri P, et al. Increased benefit of interleukin-1 inhibition on vascular function, myocardial deformation, and twisting in patients with coronary artery disease and coexisting rheumatoid arthritis. Circ Cardiovasc Imaging 2014;7(4):619–28.
[37] Gonzalez-Juanatey C, Llorca J, Vazquez-Rodriguez TR, Diaz-Varela N, Garcia-Quiroga H, Gonzalez-Gay MA. Short-term improvement of endothelial function in rituximab-treated rheumatoid arthritis patients refractory to tumor necrosis factor alpha blocker therapy. Arthritis Rheum 2008;59(12):1821–4.
[38] Kerekes G, Soltesz P, Der H, Veres K, Szabo Z, Vegvari A, et al. Effects of rituximab treatment on endothelial dysfunction, carotid atherosclerosis, and lipid profile in rheumatoid arthritis. Clin Rheumatol 2009;28(6):705–10.
[39] Mathieu S, Pereira B, Dubost JJ, Lusson JR, Soubrier M. No significant change in arterial stiffness in RA after 6 months and 1 year of rituximab treatment. Rheumatology (Oxford, England) 2012;51(6):1107–11.
[40] Hsue PY, Scherzer R, Grunfeld C, Imboden J, Wu Y, Del Puerto G, et al. Depletion of B-cells with rituximab improves endothelial function and reduces inflammation among individuals with rheumatoid arthritis. J Am Heart Assoc 2014;3(5):e001267.
[41] Benucci M, Saviola G, Manfredi M, Sarzi-Puttini P, Atzeni F. Factors correlated with improvement of endothelial dysfunction during rituximab therapy in patients with rheumatoid arthritis. Biologics 2013;7:69–75.
[42] NS Meshcherina, Knyazeva LA, Goryainov II, Knyazeva LI. Vasoprotective effects of genetically engineered biologic drugs in patients with rheumatoid arthritis. Sovremennye Tehnologii v Medicine 2015;7(3):8.
[43] Novikova DS, Popkova TV, Lukina GV, Luchikhina EL, Karateev DE, Volkov AV, et al. The effects of rituximab on lipids, arterial stiffness and carotid intima-media thickness in rheumatoid arthritis. J Korean Med Sci 2016;31(2):202–7.
[44] Kume K, Amano K, Yamada S, Hatta K, Ohta H, Kuwaba N. Tocilizumab monotherapy reduces arterial stiffness as effectively as etanercept or adalimumab monotherapy in rheumatoid arthritis: an open-label randomized controlled trial. J Rheumatol 2011;38(10):2169–71.
[45] Protogerou AD, Zampeli E, Fragiadaki K, Stamatelopoulos K, Papamichael C, Sfikakis PP. A pilot study of endothelial dysfunction and aortic stiffness after interleukin-6 receptor inhibition in rheumatoid arthritis. Atherosclerosis 2011;219(2):734–6.
[46] McInnes IB, Thompson L, Giles JT, Bathon JM, Salmon JE, Beaulieu AD, et al. Effect of interleukin-6 receptor blockade on surrogates of vascular risk in rheumatoid arthritis: MEASURE, a randomised, placebo-controlled study. Ann Rheum Dis 2015;74(4):694–702.
[47] Ruiz-Limon P, Ortega R, Arias de la Rosa I, MDC Abalos-Aguilera, Perez-Sanchez C, Jimenez-Gomez Y, et al. Tocilizumab improves the proatherothrombotic profile of rheumatoid arthritis patients modulating endothelial dysfunction, NETosis, and inflammation. Transl Res. 2017;183:87–103.
[48] Bacchiega BC, Bacchiega AB, Usnayo MJ, Bedirian R, Singh G, Pinheiro GD. Interleukin 6 inhibition and coronary artery disease in a high-risk population: a prospective community-based clinical study. J Am Heart Assoc 2017;6(3).
[49] Davignon J, Ganz P. Role of endothelial dysfunction in atherosclerosis. Circulation 2004;109(23 Suppl 1):III27–32.
[50] Shahin Y, Khan JA, Chetter I. Angiotensin converting enzyme inhibitors effect on arterial stiffness and wave reflections: a meta-analysis and meta-regression of randomised controlled trials. Atherosclerosis 2012;221(1):18–33.
[51] Haruna Y, Morita Y, Komai N, Yada T, Sakuta T, Tomita N, et al. Endothelial dysfunction in rat adjuvant-induced arthritis: vascular superoxide production by NAD(P)H oxidase and uncoupled endothelial nitric oxide synthase. Arthritis Rheum 2006;54(6):1847–55.
[52] Egi K, Conrad NE, Kwan J, Schulze C, Schulz R, Wildhirt SM. Inhibition of inducible nitric oxide synthase and superoxide production reduces matrix metalloproteinase-9 activity and restores coronary vasomotor function in rat cardiac allografts. Eur J Cardiothorac. Surg 2004;26(2):262–9.
[53] Corder R, Carrier M, Khan N, Klemm P, Vane JR. Cytokine regulation of endothelin-1 release from bovine aortic endothelial cells. J Cardiovasc Pharmacol 1995;26(Suppl. 3):S56–8.
[54] Moroni L, Selmi C, Angelini C, Meroni PL. Evaluation of endothelial function by flow-mediated dilation: a comprehensive review in rheumatic disease. Arch Immunol Ther Exp (Warsz) 2017;65(6):463–75.
[55] Simon A, Chironi G, Levenson J. Comparative performance of subclinical atherosclerosis tests in predicting coronary heart disease in asymptomatic individuals. Eur Heart J 2007;28(24):2967–71.
[56] Bergholm R, Leirisalo-Repo M, Vehkavaara S, Makimattila S, Taskinen MR, Yki-Jarvinen H. Impaired responsiveness to NO in newly diagnosed patients with rheumatoid arthritis. Arterioscler Thromb Vasc Biol 2002;22(10):1637–41.
[57] Ambrosino P, Tasso M, Lupoli R, Di Minno A, Baldassarre D, Tremoli E, et al. Non-invasive assessment of arterial stiffness in patients with rheumatoid arthritis: a systematic review and meta-analysis of literature studies. Ann Med 2015;47(6):457–67.
[58] Van Doornum S, McColl G, Jenkins A, Green DJ, Wicks IP. Screening for atherosclerosis in patients with rheumatoid arthritis: comparison of two in vivo tests of vascular function. Arthritis Rheum 2003;48(1):72–80.
[59] Van Bortel LM, Laurent S, Boutouyrie P, Chowienczyk P, Cruickshank JK, De Backer T, et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. J Hypertens 2012;30(3):445–8.
[60] Ikdahl E, Rollefstad S, Wibetoe G, Olsen IC, Berg IJ, Hisdal J, et al. Predictive value of arterial stiffness and subclinical carotid atherosclerosis for cardiovascular disease in patients with rheumatoid arthritis. J Rheumatol 2016;43(9):1622–30.
[61] Virmani R, Avolio AP, Mergner WJ, Robinowitz M, Herderick EE, Cornhill JF, et al. Effect of aging on aortic morphology in populations with high and low prevalence of hypertension and atherosclerosis. Comparison between occidental and Chinese communities. Am J Pathol 1991;139(5):1119–29.
[62] Bots ML, Hofman A, Grobbee DE. Increased common carotid intima-media thickness. Adaptive response or a reflection of atherosclerosis? Findings from the Rotterdam study. Stroke 1997;28(12):2442–7.
[63] Corrales A, Gonzalez-Juanatey C, Peiro ME, Blanco R, Llorca J, Gonzalez-Gay MA. Carotid ultrasound is useful for the cardiovascular risk stratification of patients with rheumatoid arthritis: results of a population-based study. Ann Rheum Dis 2014;73(4):722–7.
[64] Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography carotid intima-media thickness task force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr 2008;21(2):93–111. (quiz 89-90).
[65] Weber C, Noels H. Atherosclerosis: current pathogenesis and therapeutic options. Nat Med 2011;17(11):1410–22.
[66] Ursini F, Russo E, Ruscitti P, Giacomelli R, De Sarro G. The effect of non-TNF-

targeted biologics and small molecules on insulin resistance in inflammatory arthritis. Autoimmun Rev 2018;17(4):399–404.
[67] Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: executive summary: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. Circulation. 2010;122(25):2748–64.
[68] Fent GJ, Greenwood JP, Plein S, Buch MH. The role of non-invasive cardiovascular imaging in the assessment of cardiovascular risk in rheumatoid arthritis: where we are and where we need to be. Ann Rheum Dis 2017;76(7):1169–75.
[69] Flore R, Ponziani FR, Tinelli G, Arena V, Fonnesu C, Nesci A, et al. New modalities of ultrasound-based intima-media thickness, arterial stiffness and non-coronary vascular calcifications detection to assess cardiovascular risk. Eur Rev Med Pharmacol Sci 2015;19(8):1430–41.