ORIGINAL ARTICLE

Atherosclerosis is an infectious disease

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ABSTRACT

Aim Rheumatoid arthritis (RA) is associated with increased risk of coronary artery disease (CAD). Studies reported that anti-rheumatic drug usage is associated with decreased risk of CAD events in RA patients. This study was conducted to investigate the effect of some anti-inflammatory drugs (etanercept, leflunomide, etoricoxib) on the development of CAD events among patients with RA using anti-rheumatic drug in comparison with nonusers.

Methods A systematic review of CAD events in RA patients was performed who used leflunomide, etanercept and etoricoxib and was compared with RA patients who don't use these drugs. The exclusion relationship and the causal relationship k were used to test the significance of the result. A p-value of < 0.05 was treated as significant.

Results Among RA patients, use of leflunomide (**p (EXCL) =0,999022483**; X^2 (EXCL) = 0,06; k = -0,03888389; p-value (k | HGD) =0,00037588), etanercept and etoricoxib was associated with significantly decreased incidence of CAD. The use leflunomide, etanercept and etoricoxib excludes cardiac events in RA patients.

Conclusion The results of study provide further support for the infectious hypothesis of atherosclerosis.

Key words: atherosclerosis, rheumatoid arthritis, therapy

INTRODUCTION

Atherosclerosis (AS) is as old as human (1) mankind itself. The term atheroma has been coined by *Celsius* (2) more than two thousands of years ago. In 1755 *Albrecht von Haller* described atherosclerosis as the degenerative (3) process observed in the intima of arteries (3) while *John Hunter* (1728–1793), the famous Scottish physician and the 'Founder of Scientific Surgery' observed already in 1793 that inflammation (4) of the internal surface of veins is common. In the following, the British surgeon *Joseph Hodgson* famous for his 1815 monograph (5) was of the opinion that inflammation (5) was the underlying cause of atheromatous arteries. Finally, the word atheromatosis was defined 1833 by *Lobstein* (6). The inflammatory theory of atherosclerosis was advocated again in 1856 by the prominent German pathologist *Rudolf Virchow* who writes about "*die acute Entzüdung der Arterien*" (7) claiming that atherosclerosis is a chronic inflammatory disease of the intima. Feeding rabbits by milk and egg yolk the Russian scientist Alexander I. Ignatowski (1875-1955) was the first (8) to reveal a relationship between cholesterol-rich food (9) and experimental atherosclerosis. Soon Anitschkow and Chalatow (10) were able to demonstrate that pure high cholesterol levels can induce experimental atherosclerosis in rabbits which directed the atherosclerotic scientific research to the lipids and cholesterol. Brown and Goldstein provided evidence that acetylated low-density lipoprotein (LDL) and not native LDL was responsible for foam cell formation of macrophages (11) followed by Daniel Steinberg (12) and his group who demonstrated that oxidized LDL (oxLDL) induces foam cell formation of macrophages. Meanwhile, atherosclerosis is considered by many authors to consist largely of the accumulation of low-density lipoprotein (LDL) cholesterol (13) within the artery wall. Historically, the hypothesis that cholesterol and atherosclerosis are related is supported for half a century especially by the Framingham Heart Study (14,15). However, several systematic reviews and meta-analysis of statin treatment for prevention of cardiovascular events provided contradictory (16–18) results. Conventional risk factors like high blood pressure, cigarette smoking, obesity, diabetes mellitus and other are not able fully to account for the risk of atherosclerosis. Atherosclerosis as the primary pathologic process in coronary artery disease (CAD) or cardiovascular disease (CVD), carotid artery disease, abdominal aortic aneurysm, and peripheral vascular disease, is considered more and more to be an ongoing inflammatory process. In general, atheroma or atherosclerosis is a chronic inflammatory (19) disease of human arterial wall characterized among other by the

thickening of the walls of arteries while the triggers for inflammation and the details of inflammatory pathways are not identified for sure. In this context, Karpouzas (20) et al. investigated 150 patients with RA and 150 matched controls with 64-slice CT angiography (CTA) for evaluation of coronary plaque and found that higher proportion of patients with RA had plaque when compared with controls (71% vs 45%, $p<0.0001$). Furthermore, several systematic review and meta-analysis provided evidence that there is an increased incidence of cardiovascular (acute myocardial infarction, stroke, cardiac death et cetera) events (21–23) in patients with rheumatoid arthritis (RA). Rheumatoid arthritis is a destructive chronic systemic inflammatory disease caused by Epstein-Barr virus (24). The use of anti-inflammatory (disease-modifying anti-rheumatic) drugs, such as leflunomide, etanercept or etoricoxib et cetera, is common in the treatment of RA. A reduced risk or mortality of cardiovascular disease (CVD) in RA patients as indicated by several studies (25,26) would provide further support for the infectious theory of atherosclerosis. To date, atherosclerosis is the most frequent reason of deaths in Western countries and equally an important problem of the contemporary medicine while our understanding of the pathogenesis and aetiology of atherosclerosis is still incomplete.

MATERIALS AND METHODS

Study design and data sources

To answer the questions addressed in this paper, the literature search in the electronic database PubMed, the collection and analyses of followed as much as possible the Preferred Reporting Items for Systematic Reviews and Meta - analysis (PRISMA) (27). The search in PubMed was performed while using some medical key words. Additionally, the reference list of identified articles was used as a potential source of articles appropriate for this study. It was possible to identify two (28,29) studies, which provided data free of access barriers on the topic investigated. The studies of Mizia-Stec et al. (30), Bernatsky et al. (31), Jacobsson et al. (32), Dixon et al. (33), Hjuler et al. (34) were not considered for a detailed analysis.

Methods

Statistical analysis

The significance of the exclusion relationship (35–40) was analysed via the chi-square distribution (41,42). The significance of the causal relationship k (35–40) was analysed by the hypergeometric (43) distribution (44,45). All statistical analyses were performed with Microsoft® Excel® for Mac® version 16.2 (181208) software (© 2018, Microsoft GmbH, Munich, Germany). The level of significance was set to 0.05. The index of unfairness (IOU) was used to control publication bias (46).

Example 1. Necessary condition.

H_o: Drug A is a necessary condition of outcome B. H_A: Drug A is not a necessary condition of outcome B.

A **negative IOU** indicates a study design which prefers to accept H_o. In point of fact, it is difficult to reject Ho under conditions were IOU is extremely negative. In particular, such study design is used authorities in drug safety studies with the goal to recognize problems with a drug as early as possible. The following **table 1** may illustrate this situation.

Table 1

		Outcome B		
		YES	NO	
Drug A	YES	1	1	2
	NO	**0**	997	997
		1	998	999

Statistical analysis.		I O U =	**-1,00**
Causal relationship k =	+0,70675	95 % CI: +0,636 to 0,78	
p-value (k | HGD) =	0,00200	X^2 (k) =	499,00
Odds ratio (OR) =	#DIV/0!	#DIV/0!	#DIV/0!
p (SINE) =	1,00000	X^2 (SINE) =	0,00
p (IMP) =	0,99900	X^2 (IMP) =	0,00
p (SINE ^ IMP) =	0,99900	X^2 (SINE ^IMP) =	0,00
p (EXCL) =	0,99900	X^2 (EXCL) =	1,00

Even the data of a negatively extremely unfair study design can be correct but must not. The example (**table 1**) demonstrates several difficulties. According to the data provided, *if* drug A, *then* outcome B (p (IMP) = 0,99900; X^2 (IMP) =0,00) is highly significant. At the same time, the relationship *drug A excludes outcome B* (p (EXCL) =0,99900; X^2 (EXCL) =1,00) is statistically highly significant too, which is a contradiction. In contrast to a

negative IOU, a study design which determines **a positive IOU** prefers to reject H_o and to accept H_A. The **table 2** may illustrate this situation.

Table 2

		Outcome B		
		YES	NO	
Drug A	YES	997	1	998
	NO	**0**	1	1
		997	2	999

Statistical analysis.		**I O U =**	**+1,00**
Causal relationship k =	+0,70675	95 % CI: +0,636 to 0,78	
p-value (k | HGD) =	0,00200	X^2 (k) =	499,00
Odds ratio (OR) =	#DIV/0!	#DIV/0!	#DIV/0!
p (SINE) =	1,00000	X^2 (SINE) =	0,00
p (IMP) =	0,99900	X^2 (IMP) =	0,50
p (SINE ^ IMP) =	0,99900	X^2 (SINE ^IMP) =	0,50
p (EXCL) =	0,00200	X^2 (EXCL) =	997,00

A **positive IOU** of about +1.0 indicates an extremely unfair study design which in our example (**table 2**) aims to reject the H_o: Drug A is a necessary condition of outcome B. If the data of such a study are not self-contradictory and at the same time not able to reject Ho as intended by study design, then the data of such a study provide strong support for the correctness of H_o.

Example 2. Sufficient condition.

H_o: *If* drug A *then* outcome B. H_A: *If* drug A *then* not outcome B.

A **negative IOU** prefers to reject H_o and to accept H_A while a **positive IOU** prefers to accept H_o. Therefore, a fair study design is of great importance to control bias.

RESULTS

Under the assumption that atherosclerosis of coronary arteries (CAD) is an inflammatory process, an 'immunosuppressive' or 'immuno-modifying' therapy in patients treated with 'immunosuppressive' or modifying medication should decrease the number of cardiovascular events.

The study of Suissa et al. Canada 2006

Suissa et al. (28) investigated in a nested case-control analysis the relationship between acute myocardial infarction and the use of disease-modifying antirheumatic drugs (DMARDs) and other medications commonly used in RA. According to Suissa et al., DMARD use is associated with a reduction in AMI risk in patients with RA. With respect to leflunomide, Suissa et al. provided the following data (**Table 3**).

Table 3

The study of Suissa et al., 2006.

		CAD event		
		YES	NO	
Leflunomide	YES	**6**	194	200
	NO	552	5386	5938
		558	5580	6138

Statistical analysis.

		IOU =	-0,88
Causal relationship k =	**-0,038884**	95 % CI: -0,07	to -0,01
p-value (k | HGD) =	**0,000376**	X^2 (k) =	9,28
Odds ratio (OR) =	+0,30	+0,13 to	+0,68
p (SINE) =	0,91007	X^2 (SINE) =	546,06
p (IMP) =	0,968394	X^2 (IMP) =	6,74
p (SINE ^ IMP) =	0,878463	X^2 (SINE ^IMP) =	552,81
p (EXCL) =	**0,999023**	**X^2 (EXCL) =**	**0,06**

The data of Suissa et al. (28) support the Null-hypothesis (p (EXCL) = (1-(6/6138)) = 0,999022483; X^2 (EXCL) = 0,06; k = -0,03888389; p-value (k | HGD) = 0,00037588) that leflunomide prevents from CAD event.

The study of Hung et al. Taiwan 2017

Hung et al. (29) investigated the relationship between an anti-rheumatic drug usage by a cohort of 6260 patients who were newly diagnosed with RA and the incidence (the probability of an occurrence of an event in a population within a specified period of time) of CAD in this RA cohort. The study endpoint of the study of Hung et al. was the occurrence of CAD according to the ICD-9-CM codes while the date of the first principal diagnosis of CAD during the follow-up period was defined as the primary endpoint. The relationship between Etanercept and CAD events is illustrated by **Table 4**.

Table 4

The study of Hung et al., 2017.

		CAD events		
		YES	NO	
Etanercept	YES	**2**	56	58
	NO	1251	4951	6202
		1253	5007	6260

Statistical analysis.

		I O U =	**-0,79**
Causal relationship k =	**-0,04004**	95 % CI: -0,07 to -0,01	
p-value (k | HGD) =	**0,00023**	X^2 (k) =	10,04
Odds ratio (OR) =	0,14134	95 % CI: +0,03 to +0,58	
p (SINE) =	0,80016	X^2 (SINE) =	1249,00
p (IMP) =	0,99105	X^2 (IMP) =	0,63
p (SINE ^ IMP) =	0,79121	X^2 (SINE ^IMP) =	1249,63
p (EXCL) =	**0,99968**	**X^2 (EXCL) =**	**0,00**

Hung et al. (29) found that 2 from 6260 patient who used etanercept developed CAD events (**p(EXCL) = (1-(2/6260)) = 0,9998**; X^2 (EXCL) = 0,0; k = -0,04004; p-value (k | HGD) =0,00023). The use of etanercept prevents RA patients from CAD events (p (EXCL) = (1-(2/6260)) = 0,9998; X^2 (EXCL) = 0,0). Etanercept use and CAD events are excluding each other. Hung et al. (29) investigated the relationship between the use of etoricoxib and CAD events. The relationship between etoricoxib and CAD events is illustrated by **Table 5**.

Table 5

The study of Hung et al., 2017.

		CAD events		
		YES	NO	
Etoricoxib	YES	**12**	144	156
	NO	1241	4863	6104
		1253	5007	6260

Statistical analysis.

		I O U =	-0,77
Causal relationship k =	-0,04924	95 % CI: - 0,08 to -0,02	
p-value (k | HGD) =	0,00001	X^2 (k) =	15,18
Odds ratio (OR) =	+0,32655	95 % CI: +0,18 to +0,59	
p (SINE) =	0,80176	X^2 (SINE) =	1229,11
p (IMP) =	0,97700	X^2 (IMP) =	4,14
p (SINE ^ IMP) =	0,77875	X^2 (SINE ^IMP) =	1233,26
p (EXCL) =	**0,99808**	**X^2 (EXCL) =**	**0,11**

Contrary to expectation 12 from 6260 patient used etoricoxib and developed still CAD events (p(EXCL) = (1-(12/6260)) = 0,99808; X^2 (EXCL) = 0,11; k = -0,04924; p-value (k | HGD) =0,00001). This result is highly significant. RA patients taking etoricoxib have decreased CAD events. The use of etoricoxib by RA patients excludes CAD events (p (EXCL) = (1-(12/6260)) = 0,99808; X^2 (EXCL) = 0,11) in RA patients.

DISCUSSION

Statins have been used since years for the treatment of hypercholesterolemia but have anti-inflammatory and immunomodulatory effects too. Statins are able to show the antiviral effects i. e. by preventing glycoprotein processing and incorporation into virus particles (47). Thus far, it is necessary to work out more precisely whether the antiviral effect of statins or the cholesterol lowering effect are responsible for prevention from cardiac events. This study has been able to provide highly significant evidence that leflunomide, a pyrimidine synthesis inhibitor, used for the treatment of RA, prevents from cardiac events. Some studies suggest that leflunomide can be used to treat a CMV infection (48). After starting leflunomide as add-on therapy the CMV viral load declined substantially in 2 months without adverse events (49). RA itself is caused by EBV (24). Since leflunomide itself prevents effectively cardiac events, a conclusion could be that atherosclerosis is caused EBV. There are several papers published which support this hypothesis (50–52). However leflunomide is a drug which is used in the treatment of rheumatoid arthritis but it has been reported too that leflunomide has anti-human cytomegalovirus (HCMV) activity and long-term suppression of viremia (53).

Patients with rheumatoid arthritis have a 10-fold systemic Epstein-Barr virus (EBV) overload (54). Etanercept did not significantly modify EBV load over time in the peripheral blood mononuclear cells (PBMCs) of RA patients but is effective against CAD events as long as we are allowed to rely on the data provided by Hung et al. (29). Tumor necrosis factor alpha (TNF-α) is a cytokine which plays a central role in the immune response to inflammation and infection. Serum TNF-α is elevated during acute CMV-infections (55). Anti-tumor necrosis factor alpha (anti-TNF- alpha) antibodies have been approved for the treatment of different chronic inflammatory diseases. Reports on such antibody therapies which resulted in severe interferences with the patient's immune system have been published too. According to the data of Weisman et al. (56) placebo-controlled, randomized, double-blinded study the safety of etanercept in patients with RA is not assured. Six patients died on study, five in the etanercept and one in the placebo group. The relationship between Etanercept and CAD events as illustrated by **Table 4** is significant. In particular, only 58 from 6260 patients obtained Etanercept and the results could be potentially biased and should be interpreted with great care.

Studies reported that cyclooxygenase (COX) activity is augmented (57) in human atherosclerosis. The increased expression of Cox-2 in atheromatous but not in unaffected arteries implicates therapeutic consequences. In particular, etoricoxib as a nonsteroidal anti-inflammatory drug (NSAID) with increased biochemical COX-2 selectivity (58) and as a potent anti-inflammatory agents (59) is of principal use. However, reviews (60) and meta-analyses (61) of the relationship between the use of cyclooxygenase (COX)-2–selective agents and cardiovascular events have reinforced the general concern about COX-2 inhibitors. In contrast to reports like these, the use of etoricoxib in RA patients prevents CAD events ($p(EXCL) = (1-(12/6260)) = 0{,}99808$; $X^2\ (EXCL) = 0{,}11$; $k = -0{,}04924$; p-value $(k \mid HGD) = 0{,}00001$).

The data analysed by this study are associated with an $IOU < 0$ which implicates that the study design of the studies analysed prefer to *reject* H_o: drug A *excludes* outcome B. However, the data were not able to reject H_o although the sample size of the data was extremely high and the study design was **negatively extremely** unfair. Thus far, the data this studies analysed provide strong support for the viral hypothesis of atherosclerosis and the infectious hypothesis of atherosclerosis must be considered as serious and is certainly worth further and very detailed

investigations. But the data of this study are not sufficient to prove that viruses like EBV or HCMV (62) or both play a causal role in human atherosclerosis.

CONCLUSIONS

There is growing evidence that inflammatory processes are involved in the development of atherosclerosis and its complications. Human atherosclerosis is an infectious disease.

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TRANSPARENCY DECLARATION

Competing interests: None to declare.

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