

Statins in rheumatology: revisited

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An increase in cardiovascular risk (CVD), including myocardial infarction and cardiac death, accompanying such diseases as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), inflammatory spondyloarthropathies, particularly psoriatic arthritis (PsA) is currently a well-known and documented phenomenon [1, 2]. A prominent role in the pathogenesis of the rapid development of vascular atherosclerotic changes is attributed to inflammatory mediators. However, at the same time, there are reports of multiple lipid disorders [3]. Consequently, for some time now, there has been a dispute concerning the usefulness of statins in the treatment (atheromatous plaque stabilization), in the prevention of the development of atherosclerotic lesions and in the secondary prevention of cardiovascular complications in the most common inflammatory rheumatic diseases [4, 5]. In addition, it has been known some years that the effects of statins are not limited to the normalization of blood cholesterol levels. In fact, the pleiotropic activity of the drugs indicates that they exert antiinflammatory and antithrombotic effects, modulate the immune response and even have a favourable effect on bone metabolism [6].

A more in-depth knowledge of the pharmacology of these drugs, especially in terms of their antiinflammatory properties, gives a clear argument in favour of attempts to use them in such diseases as RA. The preliminary findings were promising. The results of the TARA study published in 2004 [7] demonstrated a statistically significant decrease in the values of DAS28, ESR and C-reactive protein (CRP) in patients treated with atorvastatin. However, further trials showing a beneficial effect of statins in the terms of their antiinflammatory effects and their role in reducing the risk of CVD [5] have been relatively scarce. Further verification is therefore necessary, and experts still have not specified clear-cut recommendations for using statins in this patient group [8]. In addition, the known hepatotoxicity of these drugs, and the risk of myopathy and adverse immunomodulatory processes manifested as the induction of lupus-like syndromes, polymyositis, hepatitis and even pemphigus

[6, 9], mean that extra caution has always been advised in patients suffering from autoimmune diseases and chronically taking drugs which often cause liver damage (NSAIDs, methotrexate, leflunomide).

Several years ago, in 2009, the European League Against Rheumatism (EULAR) issued recommendations about the need to assess the risk of cardiovascular diseases in RA, but also in inflammatory spondyloarthropathies [8]. The recommendations state that the evaluation of the risk can be performed on the basis of cardiac models, e.g. SCORE, taking into consideration the atherogenic index of total cholesterol/HDL-cholesterol. The calculated risk should be multiplied by 1.5 in patients with rheumatoid factor (RF) and/or ACPA, duration of the disease > 10 years and the presence of extra-articular manifestations. It was also established that statins, ACE inhibitors or AT-II receptor blockers should be used in compliance with the national standards.

However, the approval of statins does not have a provision allowing their use in the treatment of RA, and all recommendations are based on their activity normalizing the blood cholesterol level. This gives rise to the question whether statins can – and should – be used in the treatment of patients at a high cardiovascular risk and with a reduced total blood cholesterol concentration. Precisely this paradox characterizes the population of patients with active RA [3].

The treatment management guidelines to reduce cardiovascular risk [10] published in 2013 by the American College of Cardiology (ACC) and the American Heart Association (AHA) enumerate four groups of patients who should benefit from an effective statin treatment:

- patients with developed atherosclerotic cardiovascular disease,
- patients with primary high concentration of LDL cholesterol > 4.9 mmol/l,
- diabetic patients aged 40–75 years,
- patients without atherosclerosis or diabetes with LDL cholesterol concentration of 1.8–4.9 mmol/l but 10-year cardiovascular risk \geq 7.5%.

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Neither the US recommendations nor the earlier European guidelines from 2011 [11], based on the evaluation of risk according to the American algorithm and in Europe – on the SCORE function chart, mention RA as an indication for statin therapy (in contrast, the documents make a mention of diabetes which carries a similar CVD risk to RA).

In secondary prevention, e.g. after myocardial infarction, in patients with clinically diagnosed CVD, the rationale for introducing statin treatment is quite clear, and the presence (or absence) of inflammatory rheumatic disease is not the decisive factor.

Vascular lesions leading to the accelerated development of atherosclerosis and CVD risk already occur at an early stage of RA, as evidenced by carotid ultrasound and measurements of the intima-media thickness (cIMT). Based on this fact, Spanish researchers [12] have recently published a very interesting study assessing the usefulness of SCORE and local REGICOR function charts in the assessment of the risk of developing atherosclerotic cardiovascular complications in RA. They showed in a group of 370 patients with RA that both, individuals at a low cardiovascular risk determined by the two scoring systems and patients at a high risk are affected by vascular changes including an increase in cIMT and the presence of atheromatous plaques in arteries. The authors of the study conclude that neither of the risk scoring systems (i.e. the international and the Spanish ones) is suitable for the assessment of cardiovascular risk in RA patients. It would be difficult to challenge that conclusion because in addition to conventional risk factors included in popular algorithms (hypertension, smoking, age, high cholesterol level) in systemic inflammatory diseases such as RA the development of atherosclerosis preceded by vascular endothelial damage and simulation of the blood coagulation system is linked to a considerable degree to the activity of inflammatory mediators which are typically absent in such function charts and risk scoring systems. Similar doubts about the usefulness of the ACC/AHA 10-year risk scores in the assessment of the risk of developing coronary calcification in RA presented Kawai VK et al. [12]. Accordingly, if one assumes – in line with AHA/ACC guidelines [10] – that patients with developed atherosclerotic cardiovascular disease should benefit from statin treatment, the value of cIMT > 0.90 mm and/or the presence of atheromatous plaques [13] should be considered as an indication for introducing statin therapy.

It is hoped that RA, similarly to diabetes, will soon be included in the recommendations as a disease markedly increasing cardiovascular risk. However, before this happens, it would be advisable to recommend an ultrasound assessment of carotid arteries in all patients

suffering from RA, ankylosing spondylitis and PsA. The results of such an assessment could serve as a basis for considering the introduction of statin treatment.

Is it reasonable to wait until the duration of RA exceeds 10 years in order to be able to multiply the SCORE risk value by 1.5?

It is also clear that an appropriate therapy and a reduction in the inflammatory activity of the disease through the use of basic DMARDs decreases vascular damage, and statins are adjuvant medications.

Systemic lupus erythematosus and lupus-like systemic diseases of the connective tissue are diseases with a different, perhaps even more complex, pathogenesis. The question “Do all lupus patients need statins” [14] is also pertinent for this patient group. The authors of that publication also highlight the fact that there are no appropriate studies corroborating the usefulness and safety of statin treatment in lupus patients. However, since lupus often involves hypercholesterolaemia, it is recommended to maintain LDL-cholesterol concentrations below 100 mg/dl to ensure primary prevention, and < 70 mg/dl for secondary prevention. In this patient group, an ultrasound assessment of cIMT also provides information about subclinical atherosclerosis, however a limited number of trials investigating atorvastatin treatment introduced on the basis of arterial assessment in patients with lupus have failed to yield unequivocal results. Consequently, although experts do not recommend routine administration of statins to lupus patients, normalization of the LDL-cholesterol concentration is an indication for introducing lipid-lowering treatment.

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