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REVIEW ARTICLE

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Cardiovascular risk in patients with spondyloarthritis

ABSTRACT

Patients with spondyloarthritis have a higher prevalence of cardiovascular diseases compared to the general population. Increased cardiovascular risk is not only related to traditional cardiovascular risk factors but also to unconventional factors that depend on chronic inflammatory disease activity. This study aims to present currently available observation and research findings indicating the impact of various factors on cardiovascular risk in patients with spondyloarthritis and the possibility of multifaceted preventive or therapeutic action, which should result in an improved prognosis of patients.

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KEY WORDS: spondyloarthritis; cardiovascular diseases; cardiovascular risk

INTRODUCTION

Spondyloarthritis (SpA) are a heterogeneous group of chronic inflammatory diseases of the osteoarticular system, with predominant involvement of sacroiliac joints and axial skeleton and the possibility of peripheral manifestations: arthritis, enthesitis, dactylitis and extra-articular manifestations, among which acute anterior uveitis (AAU), inflammatory bowel disease (IBD), psoriasis are the most common. SpAs are systemic diseases in the course of which, due to a chronic inflammatory process, damage may occur not only to components of the musculoskeletal system but also to extra-articular organs and tissues. Cardiovascular disease (CVD) is one of the serious extra-articular complications that occur in SpA patients, significantly affecting the quality and length of life and prognosis of patients [1].

The incidence of CVS diseases is more common among SpA patients compared to the general population, including coronary artery disease (CAD), heart failure (HF), cerebrovascular disease, peripheral vascular disease (PVD), and atherosclerosis which underpins the development of CVD. CV mortality rates are also higher in SpA patients compared to the general population [1, 2].

According to the updated Assessment of SpondyloArthritis International Society — European Alliance of Associations for Rheumatology (ASAS-EULAR) recommendations for the management of axial SpA (axSpA), the first-line therapy for SpA continues to be non-steroidal anti-inflammatory drugs (NSAIDs), the use of which in the general population is associated with increased hazard ratio (HR) of cardiovascular (CV) events. In the case of an absent or insufficient therapeutic effect, biologics or Janus kinase inhibitors (JAKi) should be considered. To date, there are limited observations and experience from clinical practice on the effects of biologics and JAKi on the cardiovascular system (CVS) [3].

The study aims to discuss the factors that affect the increase in HR of CV events in SpA patients and present the currently available research results and clinical observations on the effect of SpA therapy on the HR of CV events.

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CVD MORBIDITY AND MORTALITY RATES AMONG SPA PATIENTS

In recent years, there has been a growing interest in and observational data have been published on the HR of CV events and CV mortality among SpA patients. A recent meta-analysis, based on the observation of a large population group, revealed an increased CVD risk and CV mortality in patients with SpAs [ankylosing spondylitis (AS), psoriatic arthritis (PsA), undifferentiated spondyloarthritis (USpA)], compared to the general population [3]. There was a significantly higher risk of myocardial infarction (MI) [relative risk (RR): 1.52; 95% confidence interval (CI): 1.29–1.80] and stroke (RR: 1.21; 95% CI: 1.0–1.47) in SpA patients, while the all-cause mortality risk was not statistically significantly increased (RR: 1.23; 95% CI: 0.96–1.57) [2]. A Spanish population study found that, among patients with inflammatory rheumatic diseases, AS patients had the highest risk of a first CV event during 5 years of follow-up (HR: 4.6, 95% CI: 11.32–15.99) but without an increased risk of CV mortality [4].

Based on large databases in the United States, CVS diseases were found to be more common in PsA patients and AS patients compared to the general population, with the following prevalence rates: CVD (1.3; 1.2), atherosclerosis (1.4; 1.5), PVD (1.6; 1.6), chronic HF (1.5; 1.8), and cerebrovascular disease (1.3; 1.7), respectively [5].

In a Swedish population-based study, the HR of acute coronary syndrome was significantly higher in patients with AS [1.54 (1.31–1.82)], PsA [1.76 (1.59–1.95)] and USpA [1.36 (1.05–1.76)] compared to the general population. The HR of acute coronary syndrome (ACS) was significantly lower in women with AS compared to women with PsA [0.59 (0.37–0.97)]. The HR of stroke was significantly higher in patients with AS [1.25 (1.06–1.48)] and PsA [1.34 (1.22–1.48)], and slightly higher in patients with USpA [1.16 (0.91–1.47)], compared to the general population. The HR of venous thromboembolism (VTE) in patients with AS, PsA, USpA was similar and significantly higher (by approximately 50%) compared to the general population [6].

RISK FACTORS CONTRIBUTING TO HIGHER HR OF CV EVENTS IN SPA PATIENTS

There are many factors that affect the increase in HR of CV events in SpA patients.

Unconventional factors, i.e. those associated with chronically active inflammatory disease, are of great importance. These include long-term persistent inflammation, which is a known accelerator of vascular atherosclerosis. Furthermore, SpA patients may have clinical manifestations of CVS involvement, which also contribute to a higher HR of CV events [1].

Traditional CV risk factors (smoking, hypertension [HTN], dyslipidemia, obesity, diabetes), which are responsible for more than 50% of all CV deaths, also play an important role. The risk of developing CVD increases with the number of traditional risk factors present in the patient. The odds ratio (OR) for a given number of risk factors present was determined: OR = 2.4; 4.2; 4.9; 7.2 for 1, 2, 3, 4 or more risk factors, respectively, compared with no traditional risk factors [7].

In a population-based retrospective study in Taiwan, 947 AS patients and almost 3,900 controls were studied for risk factors for major cardiovascular events (MACEs), which included MI, ischaemic stroke, the need for coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). The incidence of MACEs was associated with the use of selective cyclooxygenase-2 inhibitors (COX-2i), i.e. coxibs (especially if the total number of daily doses is > 132 in the preceding year) and glucocorticosteroids (GCSs), as well as residence in rural regions, and the presence of comorbidities [diabetes, HTN, hyperlipidemia, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), chronic HF, valvular heart disease]. The development of MACEs was not associated with the use of non-selective NSAIDs, preferential COX-2i, biologics, methotrexate (MTX), sulfasalazine (SS), or extra-articular manifestations of SpA [8].

TRADITIONAL CV RISK FACTORS

Smoking

Currently, there is no doubt that smoking has a negative impact on the activity of axSpA and the severity of the disease course [1]. In a French population of patients with early-onset SpA (DESIR), smoking was found to be associated with early disease onset, high activity, increased inflammatory process, greater structural damage visible on radiographs (X-rays) and poorer quality of life in patients [9].

Smoking prevalence in SpA patients varies in different populations; in the COMOSPA

study, smoking prevalence ranged from 6% to 44% (mean 29%) [10].

According to current ASAS-EULAR recommendations, smoking is a risk factor for spinal inflammatory disease and disease progression in axSpA. There have been no scientific studies to date to assess the beneficial effect of smoking cessation on the progress of axSpA. However, even in the absence of such evidence, it seems reasonable to recommend smoking cessation to every patient based on well-known adverse effects of smoking [3].

Hypertension (HTN)

HTN is estimated to be more common in SpA patients. According to data from the United States, the prevalence rate of HTN in AS and PsA patients is 1.3 compared to the general population [5]. In the international COMOSPA study, HTN was found in 34% of SpA patients, particularly in patients from Northern European countries [9]. The prevalence of HTN in PsA patients is higher compared to the general population (OR = 1.37–1.51), as well as compared to patients with psoriasis (29% *vs.* 18%) [11].

The development of HTN in SpA patients may be related to chronic NSAID therapy. The risk of developing HTN is 12% higher in patients continuously taking NSAIDs compared to patients taking NSAIDs temporarily (in case of pain) [12].

Dyslipidemia

In the international COMOSPA study, hypercholesterolemia was found in 27% of SpA patients [10]. According to data from the United States, the prevalence rate of hyperlipidemia in AS and PsA patients is 1.3 compared to the general population [5]. Dyslipdemia was observed more frequently in PsA patients compared to patients with psoriasis (28% *vs.* 13.5%) [11].

In the course of a chronic inflammatory process, there are changes in the lipid profile,

which include reduced cholesterol levels in the high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) fractions, and an increased value of the atherogenic index (total cholesterol/HDL-C). There are also qualitative changes, including a pro-atherogenic HDL-C profile, LDL oxidation. All these changes are associated with a higher HR of CV events in SpA patients [1].

Obesity

In the Dutch population, in axSpA patients compared to the general population, obesity [body mass index (BMI) ≥ 30 kg/m^2]) was more common (22% *vs.* 15%, respectively) and overweight less common (BMI ≥ 25 < 30 kg/m^2) (37% *vs.* 43%). AxSpA patients with obesity or overweight were older, with longer disease duration and complications, especially HTN. Obese patients were reported to have higher disease activity, poorer quality of life and worse physical performance [13].

Most observations indicate a higher prevalence of obesity in PsA patients compared to the general population; in one population-based study, 44% of PsA patients were found to be obese [11]. Obesity is more common in PsA patients compared to AS patients [14].

Diabetes

According to data from the United States, the prevalence rate of diabetes in AS and PsA patients is 1.2 and 1.5, respectively, compared to the general population [5]. In the international COMOSPA study, diabetes was found in 8.8% of SpA patients [10]. Patients with PsA often have insulin resistance (approximately 16%), type 2 diabetes (T2D) (6–20%) [11].

Metabolic syndrome

Patients with axSpA had a higher prevalence rate of metabolic syndrome [according to National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) criteria] compared to controls, 45.8% *vs.* 10.9% [1].

Metabolic syndrome occurs in 24-58% of PsA patients, more frequently than in the general population and compared to AS patients (OR = 2.44). Metabolic syndrome and its individual components are found significantly more frequently in PsA patients compared to patients with psoriasis [11].

UNCONVENTIONAL CV RISK FACTORS ASSOCIATED WITH INFLAMMATION

The significantly higher HR of CV events occurring in SpA patients compared to the general population is related to the severity of the inflammatory process that accompanies active inflammatory disease. Chronic inflammation induces accelerated atherosclerosis, which may result in the development of CV events.

Relationships in PsA patients

In a prospective follow-up (median 9.9 years) of PsA patients, a higher risk of developing CV events was associated with higher values of the disease activity index for psoriatic arthritis (DAPSA) and the presence of atherosclerotic plaques of carotid intima-media thickness (cIMT) on ultrasound (US) [15].

It was also found that in PsA patients, elevated C-reactive protein (CRP) levels at first assessment were associated with indicators of poor prognosis, including the development of erosions, sacroiliitis, the need for biologics [tumour necrosis factor alpha inhibitors (*TNFi*)], more comorbidities. In contrast, the group of patients with normal CRP levels during long-term follow-up had a milder form of the disease. It was implied that elevated CRP levels might be indicative of a more severe form of the disease in the course of PsA, often requiring TNFi treatment [16]. Another retrospective study found that persistently elevated CRP levels (particularly > 3 mg/l) during follow-up were significantly associated with a higher CV risk (HR = 1.02) [17].

It was also found that PsA patients (but not AS patients) had elevated levels of interleukin-18 (IL-18), which was associated with higher disease activity and a pro-atherogenic lipid profile, and consequently a higher HR of CV events. The authors pointed to IL-18 as being important in the pathogenesis of SpA and a possible therapeutic target [18].

Relationships in AS patients

The Ankylosing Spondylitis Disease Activity Score — CRP (ASDAS-CRP) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) were shown to be associated with CV risk in axSpA patients. Disease activity, as assessed by ASDAS-CRP, was significantly higher in patients with 1 (OR = 2.0) or ≥ 2 (OR = 3.39) CV risk factors compared to patients without CV risk factors. The BASDAI value was also higher in patients with more CV risk factors [7].

In AS patients, it was found that structural damage visible on X-ray was associated with the presence of atherosclerotic plaques and a higher HR of CV events, irrespective of disease duration, age, smoking [19].

Computed tomography angiography (CTA) revealed atherosclerotic lesions in coronary arteries significantly more often in AS patients compared to controls (48.7% *vs.* 26.3%). There was a significant relationship between atherosclerotic lesions and the age of patients, HTN and dyslipidemia [20].

Assessment of atherosclerotic lesions on carotid artery Doppler ultrasound

The accepted method for identifying subclinical or advanced atherosclerosis is cIMT ultrasound and assessment of the presence of atherosclerotic plaques. This examination can be used for monitoring the patient during the course of the disease and treatment.

Subclinical atherosclerosis in the form of higher cIMT value (0.74 mm *vs.* 0.67 mm, respectively) and advanced atherosclerosis with plaques (29.7% *vs.* 9.4%, respectively) were significantly more frequent in AS patients without clinical manifestations of CVD, compared to controls. Predictive factors for the occurrence of atherosclerotic plaques were the ESR value at diagnosis (OR = 1.18) and duration of the disease (OR = 1.04). There was no association of ESR or CRP with cIMT values [21]. In the group of SpA patients (mean age 43.9 years, disease duration 7.8 years), the mean cIMT value was 0.77 mm and ultrasound signs of atherosclerosis were found in 17.5% of patients [22].

Comparable severity of atherosclerotic lesions was found in AS patients and the non-radiographic form of axSpA (nr-axSpA). Following cIMT ultrasound, more than 40% of patients who were initially classified as moderate CV risk patients according to the Systemic Coronary Risk Evaluation (SCORE) scale were categorised as very high CV risk patients [23].

Another study that compares SpA and rheumatoid arthritis (RA) patients found no significant differences in terms of cIMT when both diseases were in remission or had low activity. For moderate to severe disease activity, the cIMT value was significantly higher in RA patients compared to SpA patients, regardless of age, disease duration, traditional CV risk factors. There was no association between cIMT and CRP in SpA patients [24].

DRUGS USED IN THE TREATMENT OF SPA AND THE CV RISK

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

NSAIDs are still the first-choice medications in the treatment of axSpA after individual consideration, for each patient, of the risks

and benefits associated with the use of these drugs [3].

The CV risk associated with NSAIDs in the treatment of SpA is still controversial. In the follow-up of AS patients, independent factors associated with reduced life expectancy (mainly due to CV causes) were diagnostic delays (OR = 1.05), elevated CRP levels (OR = 2.68), inability to work (OR = 3.65) and non-use of NSAIDs (OR = 4.35) [25]. A population-based study proved that in AS patients aged ≥ 65 years, lack of NSAID use was one of the factors associated with increased CV mortality rate [26].

Another retrospective study in PsA patients found that exposure to NSAIDs was significantly associated with a lower risk of CV events (HR = 0.38) [17].

NSAIDs appear to reduce the HR of CV events by controlling the inflammatory process. Therefore, non-use of NSAIDs may be associated with the progression of atherosclerosis. However, it should be taken into account that the results obtained in this study may be the effect of recommending NSAIDs only to patients without current CV risk factors [1].

CONVENTIONAL SYNTHETIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

Sulfasalazine (SS)

It appears that SS may have a protective effect on CV risk. A population-based, retrospective study in Taiwan found that SS reduced the CVD risk in AS patients (HR = 0.65) [27].

Methotrexate (MTX)

Observations of PsA patients indicate a beneficial effect of MTX treatment on metabolic factors (reduction in the prevalence of diabetes, dyslipidemia, obesity) and thus a reduced HR of CV events [10].

BIOLOGIC DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS (BDMARDS)

The introduction of biologics into the treatment of SpA represented a huge advance in treatment due to the effective inhibition of the inflammatory process. An additional effect may be a reduction in the HR of CV events.

TNF inhibitors (TNFi)

TNFi have beneficial effects on IMT, endothelial dysfunction and have a stabilising effect on atherosclerotic plaques [28]. In a group of AS patients, it was found that in those who were continuously treated with TNFi, the cIMT value did not change significantly after almost 5 years of follow-up, whereas in those who terminated TNFi treatment early (15% of patients), there was a significant increase in cIMT (+0.057 mm, p = 0.069). The effect of TNFi was mainly associated with a significant reduction in disease activity [28]. The results of the meta-analysis seem to indicate that TNFi have preventing effects in AS, PsA, RA patients who respond well to treatment, and there is even suggested evidence of reversing the progression of IMT and subclinical atherosclerosis. However, it is uncertain whether this is a TNFi-specific effect or it remains related to good control of the inflammatory process, regardless of the therapeutic strategy used [29].

In PsA patients treated with TNFi for an average of 52 months, there were fewer atherosclerotic plaques and lower cIMT values compared to patients treated with conventional DMARDs. The duration of TNFi therapy correlated with the cIMT value, indicating a cumulative effect of TNFi treatment [30].

In a large cohort of SpA patients, TNFi-treated patients compared to TNFi-untreated patients had a reduced risk of MACEs (HR = 0.37) and stroke/*transient ischaemic attack* (TIA) (HR = 0.21) [31]. In another study in axSpA patients, TNFi treatment was not associated with a reduction in the risk of CVD. According to the authors, the observed beneficial effect on CVS depended on a reduction in the severity of the inflammatory process and not on the specific action of TNFi on CVDs in SpSA [32].

The lipid profile may change during TNFi therapy. According to reports in the literature, the atherogenic index did not change in axSpA patients during infliximab treatment, while there were improvements during therapy with etanercept [1].

Observational studies in PsA patients treated with TNFi showed a reduced risk of diabetes (OR = 0.62), compared to therapy with other non-biologics (except MTX). TNFi therapy was also found to have a beneficial effect on components of the metabolic syndrome (waist circumference, levels of HDL-C, triglycerides, glucose) [10].

Interleukin 17 inhibitors (IL-17i)

There is currently much less experience of the effects of IL-17i due to their shorter duration of use in SpA patients. IL-17A has

an adverse effect on cells of the vascular wall and heart, showing proinflammatory, procoagulant, and potentially proatherogenic actions. It appears that IL-17i should have a beneficial effect on HR of CV events [1].

In clinical trials evaluating the efficacy of therapy with secukinumab or ixekizumab, there was no increase in CV events [1]. In a large study based on French databases, a small number of MACEs were found in PsA patients treated with bDMARDs. The risk of MACEs was higher in patients who started IL-12/23i or IL-17i therapy compared to TNFi therapy [33].

TARGETED SYNTHETIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (TSDMARDS)

Janus kinase inhibitors (JAKs) represent a new class of drugs in SpA treatment recommendations. Tofacitinib and upadacitinib are currently approved for the treatment of SpA patients [3]. The data on these drugs come mainly from clinical trials. In RA patients, it was found that treatment with tofacitinib, compared to treatment with TNFi, was associated with a higher risk of MACEs. Therefore, the current ASAS-EULAR recommendations indicate the need to limit the use of JAKi in patients older than 50 years of age and with at least one CV risk factor and in patients older than 65 years of age [3].

CONCLUSIONS

SpA patients have a significantly higher HR of CV events compared to the general population. This is related to the simultaneous interaction of multiple factors, including traditional CV risk factors, factors associated with chronic inflammation and the possible adverse effects of the therapy used. The active inflammatory process appears to be the decisive factor, so the most effective method of reducing the HR of CV events is effective treatment aimed at achieving remission of the disease.

CONFLICT OF INTERESTS

Author declare no conflict of interest.

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