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TREATMENT OF HYPERTENSION IN PATIENTS WITH RHEUMATIC DISEASES

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Introduction

Among "rheumatic" diseases rheumatoid arthritis (RA) is the most common immune-inflammatory disorder characterized by symmetric polyarthritis affecting predominantly the small joints of the hands and feet. In patients with seropositive RA, the disease course is more aggressive, extra-articular manifestations are more frequent and their mortality is increased. Osteoarthritis (OA) is one of the most common causes of disability in adults. It is caused by chronic damage of the cartilage in joints - large ones are most frequently involved. Beyond them, gout deserves special attention since it has multiple interactions with hypertension or its treatment.

Hypertension in patients with rheumatoid arthritis

The prevalence of hypertension is substantially (by about 42%) higher in RA than in the average population [1]. Among patients with RA the prevalence of hypertension is estimated to 52–73% [2, 3], and the proportion of well-controlled patients is much lower, at 13.2%, than in the general population, where it is estimated to be around 30%, but large differences were found in different populations. Both cardiovascular (CV) morbidity and mortality are increased in RA compared to controls, which is only partially attributable to traditional CV risk factors [4, 5], so RA can be characterized as a disease with high CV risk, similarly to diabetes mellitus and chronic kidney diseases.

This increased prevalence of hypertension in patients with RA can be explained by several factors: systemic and low-grade inflammation, physical inactivity and medication (e.g. corticosteroids and non-steroidal anti-inflammatory drugs (NSAID) used for the control of disease activity and its symptoms.

Inflammatory burden plays a pivotal role in the observed excess CV risk [6]. Increased high-sensitivity C-reactive protein (hsCRP) levels representing systemic inflammation are characteristic for patients with RA. Low-grade systemic inflammation can lead to hypertension via several mechanisms: reduction of nitric oxide production in endothelial cells leads to vasoconstriction, increased production of endothelin-1, and platelet activation. Moreover, CRP is able to up-regulate the expression of angiotensin type-I (AT1) receptors thus activating the renin-angiotensin system (RAS) [7]. As a consequence, systemic vascular resistance is increased in RA while elasticity of small and large arteries is reduced. These processes together with the increased arterial stiffness, also observed in RA, may lead to increased arterial blood pressure [7]. These processes together with the increased arterial stiffness, also observed in RA, may lead to blood pressure elevation [7], increased shear stress and activation of inflammatory cascade.

Patients with RA are limited in physical activity, which can be explained by chronic pain and joint damage. Lack of exercise may lead to overweight in some patients, and subsequently, hypertension. In addition to these pathophysiological processes numerous drugs used in RA (NSAIDs, glucocorticoids) can also increase blood pressure and inhibit the antihypertensive effect of drugs, such as diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) (*see later*).

Hypertension in patients with osteoarthritis

The prevalence of both OA and hypertension significantly increases with growing age. OA and hypertension often coexist in patients. It is very important to highlight that nowadays even patients over 80 years old can benefit from lowering blood pressure [8]. In a large cohort of patients with osteoarthritis, 57.6% were reported to take antihypertensive medication [9].

Sedentary lifestyle caused by OA, and the subsequent overweight, further aggravates this situation. Moreover, pharmacological treatment used for the management of OA (see in RA) is also able to increase blood pressure, as will be discussed later in detail.

Special aspects of the management of hypertension in patients with rheumatic diseases

Non-pharmacological treatment

Risk assessment

Cardiovascular risk stratification should be performed with special considerations in patients suffering from RA. There are several recommendations about how the presence of RA should be considered when categorizing individuals into different CV risk groups.

RA should be regarded as an independent risk factor for hypertension [10]. It was suggested to add "+1" to the total sum of risk factors in RA patients with hypertension [7] when using European Society of Cardiology/European Society for Hypertension (ESC/ESH) guidelines [11]. On the other hand, the latest European League Against Rheumatism (EULAR) recommendations for CV risk management compose a subset in RA patients defined if patients meet at least two of the following three criteria:

- disease duration of more than 10 years;
- rheumatoid factor or anti-cyclic citrullinated peptide (anti-CCP) positivity;
- presence of certain extra-articular manifestations.

For the aforementioned patient population, risk score models should be adapted by applying a 1.5 multiplication factor [12].

Lifestyle modifications

Beyond efforts for the access and maintenance of ideal body weight, regular physical activity, reduction of sodium intake and other dietary considerations, probably the most important recommendation for an RA patient is smoking cessation. There is now clear evidence that several factors (citrullination of autoantigens, changes in cytokine balance, increased risk of infections) link cigarette smoking to the development and more aggressive disease course of RA (predominantly the seropositive form) [13].

Pharmacological treatment

The impact of antirheumatic drugs on blood pressure

Non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxigenase-2 inhibitors (coxibs)

Non-selective NSAIDs and coxibs are commonly used both in RA and in OA. In an earlier meta-analysis, including 50 trials, NSAIDs caused an average of 5 mm Hg elevation in systolic blood pressure. The most pronounced increase in blood pressure was observed during treatment with piroxicam, indomethacin and naproxen [14]. A more recent systematic review demonstrated a significant increase in mean blood pressure values after at least 4-weeks use of ibuprofen and indomethacin, compared to placebo. After treatment with naproxen, sulindac, nabumetone and diclofenac, blood pressure also increased but the difference did not reach statistical significance. On treatment with ibuprofen, relative risk of development of hypertension was 2.85 (CI: 1.4–5.6). The blood pressure increasing effect of non-selective NSAIDs was more obvious in hypertensive than in normotensive patients [15]. Possible mechanisms in the background can be salt and water retention by decreased prostaglandin production in the renal arteries and subsequently increased antinatriuretic effect in the macula densa, increased peripheral vascular resistance by promoting endothelin-1 and inhibiting vasodilatory prostaglandin synthesis [16].

Several studies have revealed that co-administration of non-selective NSAIDs with diuretics, beta-receptor blockers, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) result in attenuation of the anti-hypertensive effect. Interestingly, this effect cannot be observed with calcium channel blockers (CCBs) [17, 18].

Selective cyclooxygenase-2 inhibitors (coxibs) were developed to decrease the risk of gastrointestinal bleeding in patients who require NSAIDs. However, after a few years it became obvious that coxibs shift the antithrombotic--prothrombotic balance in the direction of the prothrombotic way by inhibiting the synthesis of prostacyclin and thereby changing the balance between vasodilatory/vasoconstrictor (thromboxane) synthesis in endothelial cells. They markedly increase systolic more than diastolic blood pressure. As a consequence of these processes, they are associated with increased cardiovascular risk (acute coronary syndrome, stroke). Based on the results of a meta-analysis composed of 19 studies, coxibs are seen to induce more pronounced elevation of blood pressure than non-selective NSAIDs or placebo [19]. A meta-analysis showed that rofecoxib (HR: 2.80), a celecoxib (HR: 2.57), ibuprofen (HR: 1.50), diclofenac (HR: 2.40) and other NSAIDs (HR: 1.29) increased CV mortality [20]. This effect was dose-dependent. In another meta-analysis involving 114 clinical studies and data from 16,094 patients, rofecoxib dose dependently increased the risk of arrhythmia (RR: 2.90), renal impairment (RR: 1.53), peripheral oedema (RR: 0.83) and hypertension (RR: 1.55). On the other hand, in patients treated with celecoxib, the risk of renal dysfunction (RR: 0.61) and hypertension was smaller than in controls [21]. In the largest meta-analysis published so far of 1,028,437 patients, the data showed that the largest increase in CV mortality was found in patients treated with diclofenac (OR:1.91) and COX-2 selective rofecoxib (OR: 1.66), and this deleterious effect of diclofenac was larger than that of rofecoxib. There was a tendency by ibuprofen to increase non-lethal stroke (OR: 1.29). On the other hand, naproxen did not increase CV mortality (OR: 0.84; NS) [22]. These data suggest that none of the NSAIDS are considered to be safe; however, it also became evident that cox-selectivity is not responsible for associated increased CV risk, which is considered as a class effect of this group of drugs. This side effect is related to the baseline CV risk of the patient; in those with higher baseline risk the deleterious side effect of NSAIDs is more pronounced [23]. The cox-2 selectivity is important only for

having less gastrointestinal bleeding, which is still the most significant side effect of NSAIDs. Coxibs are especially unfavourable in patients with heart failure, impaired renal function and liver cirrhosis. According to the latest findings, among coxibs, only rofecoxib was associated with hypertension, so the class effect for this group of agents is not evident [7].

Extensive research is being conducted in order to generate nitric oxide (NO)-donating molecules, which provide the beneficial effects of the base molecule (mainly NSAIDs) while releasing NO to neutralize the harmful effects of the original agent [24]. One of these emerging new molecules is naproxcinod (naproxen joined via a linker to NO), which produces a statistically significant systolic blood pressure decrease compared to naproxen [25].

Taken together, if their use cannot be avoided, NSAIDs and coxibs have to be used with close monitoring of blood pressure, and if initiation or modification of antihypertensive treatment is necessary, CCBs should be chosen.

Glucocorticoids (GC)

Although GCs can be administered intra-articularly in OA patients with severe and treatment-resistant pain, their main application area is the systemic route in inflammatory rheumatic diseases such as RA. The blood pressure elevating effect of sustained GC treatment has been known for a long time. Use of even a moderate dose of prednisolon (> 7.5 mg/day) over more than 6 months elevates blood pressure and increases the incidence of hypertension [7]. The BP-increasing effect of GCs is dose-dependent, as it was shown that use of a low-dose (≤ 7.5 mg/day) of prednisolon-equivalent, even for a long time (at least 4 years), resulted only in a trend for increased blood pressure compared to untreated patients [26].

In the latest EULAR recommendations, two opposite ways are mentioned about how GCs influence CV risk in patients with RA: at first, due to their well-known harmful effects on lipids, glucose tolerance and obesity, corticosteroids could elevate CV risk, and secondly, they can even decrease it by suppressing inflammation and decreasing pain [12].

Disease-modifying antirheumatic drugs (DMARDs)

Leflunomide induces hypertension in 2-4.7% of patients, presumably by increasing sympathetic tone [7]. Cyclosporin is known to trigger hypertension, and it is contraindicated in patients with uncontrolled hypertension. There are several hypotheses for the explanation of cyclosporin-induced hypertension: by enhancing endothelin-related vasoconstriction, by reducing nitric oxide and suppressing prostacyclin production, and by reducing the glomerular filtration rate and causing sodium retention. Cyclosporine-induced hypertension should be treated with CCBs (diltiazem and verapamil are preferred because they increase plasma cyclosporin levels). Reduction of the dose or withdrawal of cyclosporin may be possible if hypertension becomes treatment-resistant [7, 27].

Biological therapies

Although there are few observations so far, no evidence exists to suggest any impact on hypertension, or on the effects of antihypertensive medication during treatment with such agents (TNF-alpha inhibitors, rituximab, anakinra, abatacept). Moreover, the potential future use of the anti-human IL-6 receptor antibody tocilizumab has been suggested to treat recalcitrant hypertension [28].

The impact of antihypertensive drugs on rheumatic diseases

Concomitant medication of patients must be carefully assessed before the initiation of any antihypertensive treatment. Patients with RA have increased sympathetic activity, which may result in high plasma renin activity. Therefore, antihypertensive treatment with ACEIs seems to be reasonable. Moreover, ACEIs suppress proinflammatory mediators such as reactive oxygen species (ROS) and CRP, and promote the expression of some anti-inflammatory factors [29]. The chronic systemic inflammation observed in RA leads to down-regulation of beta-adrenoceptors and L-type calcium channel-related ion currents but does not change the expression of angiotensin II type I receptors. Theoretically, these effects may attenuate the therapeutic efficacy of beta-blockers and CCBs, but no change is expected in the blood pressure lowering effect of ARBs [30]. Since insulin resistance — especially under sustained GC treatment — is frequent, use of conventional non-cardioselective beta-blockers and thiazides should be avoided [31]. If Raynaud's phenomenon is associated with RA, selective beta-blockers should be avoided while ACEIs, ARBs, CCBs, carvedilol or nebivolol might be preferred [7].

Gout

Gout is characterized by severely painful inflammatory attacks caused by the accumulation of monosodium urate monohydrate crystals in the joints and their surroundings. The development of crystal deposits in the affected joints is promoted by high serum uric acid levels. A typical acute gout attack most often involves the first metatarsophalangeal joint, which is known as podagra. However, gouty arthritis can occur in other joints including the ankles, knees, elbows, wrists and fingers. Symptoms of acute attacks are represented by rapid onset of intensive pain, accompanied by local swelling, warmth and hyperaemia. The increased level of uric acid is the result of a disturbed purine metabolism. Hyperuricaemia can be of primary or secondary origin, and both can be caused by under-excretion or overproduction of uric acid. The actual level of serum uric acid is defined by the proportion of production and secretion. In the majority of patients, hyperuricaemia is caused by diminished uric acid secretion in the renal proximal tubules. Obesity, a purine-rich diet and excessive alcohol consumption contribute to hyperuricaemia by overproduction of uric acid. An elevated uric acid level does not necessarily cause gout, but even a less pronounced elevation is able to raise cardiovascular risk by impairment of endothelial function.

Non-pharmacological modalities to decrease serum uric acid levels include dietary purine restriction, normalization of body weight, abundant fluid intake and discontinuation of predisposing diuretics (mainly thiazides).

Regarding pharmacological treatment, uricostatic allopurinol is still used as the gold standard; it interferes with uric acid production by blocking xanthine oxidase enzyme. Although thiazide diuretics are keystones of modern management of hypertension, they are proven to elevate serum uric acid levels in a dose dependent manner and may provoke gouty arthritic attacks if applied in higher doses. Such a deleterious effect of indapamide is not known. A recent meta-analysis of data from 24,768 patients with gout and of 50,000 controls showed that chronic treatment of hypertension with diuretics, beta-blockers and — as a surprise — with ACEIs and non-losartan ARBs increased the incidence of gout in hypertensive patients, but calcium antagonists and losartan decreased it [32]. For the treatment of hypertension of patients with hyperuricaemia, losartan and calcium antagonists, as amlodipine should be preferred. Losartan increases urate secretion by the inhibition of urate/anion exchange in the renal proximal tubules. As both secretion and post-secretory reabsorption is blocked, the rate of uric acid excretion rises from 10 to 30% [33, 34]. This is a molecule-specific attribute, which cannot be observed in any other ARBs. Amlodipine also slightly increases uricosuria by increasing the glomerular filtration rate and, consequently, the clearance rate of uric acid [35].

Conclusions

Patients with chronic rheumatic diseases are considered to be at high CV risk, and this condition is frequently associated with hypertension. Treatment with NSAIDs further increases CV risk (acute coronary syndromes, stroke); therefore, this type of therapy should be carried out with close observation of patients and for the shortest possible duration. In patients with hyperuricaemia, uricosuric antihypertensives such as losartan and CCBs are preferred and thiazides or beta-blockers should be avoided.

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