Cardiovascular risk in patients with plaque psoriasis and psoriatic arthritis without a clinically overt cardiovascular disease: the role of endothelial progenitor cells

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Abstract
Psoriasis is an autoimmune, chronic disease determined by environmental and genetic factors. The occurrence of psoriasis is accompanied by metabolic diseases, cardiovascular diseases (CVD) and depression, disturbances on interpersonal interactions and a tendency towards social isolation. Regardless of the form of psoriasis and the severity of the disease, early arterial lesions are recorded in arterial vessels of patients. Nevertheless, the chance of CVD is higher in the population of patients with severe psoriasis than in patients with mild to moderate psoriasis. The correlation between the presence of atherosclerotic plaque and psoriatic plaque is partially explained by: (1) a similar inflammatory pathway – via the T helper cells, (2) impaired angiogenesis, and (3) endothelial dysfunction. In the considered tests, the diagnostic tools used showed a reduced level of endothelial progenitor cells in the circulation of patients with psoriasis. Endogenous angiopoietin stimulation in patients with psoriasis leads to deterioration of endothelial regeneration, atherosclerosis which secondarily contributes to the progression of heart failure. Clinical and experimental data confirm the potential of immunomodulatory methods to combat both autoimmune and cardiovascular diseases through the use of immunosuppressive drugs. Full understanding of the way in which CVD develops in patients with autoimmune diseases would enable the implementation of targeted cell therapy allowing the quality and life expectancy of patients to be improved. Modern cellular diagnostic tools allow the use of highly specific biomarkers, which in the near future will enable a reduction in morbidity and mortality due to CVD.

Key words: psoriasis, atherosclerotic, cardiovascular diseases, cellular diagnostics, biomarkers.

Introduction
Psoriasis is a genetically determined chronic inflammatory disease triggered by many environmental factors (e.g. trauma, infections, medications, psychological stress) which affects nearly 2% to 4% of the world’s population. The most common form of the disease is plaque psoriasis – it accounts for 80% to 90% of all cases [1, 2]. In 75% of cases psoriasis is diagnosed before the age of 40; most often between the age of 16 and 22. During the course of the disease, excessive proliferation, accelerated growth and abnormal maturation of epidermal cells become visible. Sharply demarcated, scaly, erythematous plaques characterize the most common form of psoriasis. The lesions are mainly located on the scalp, elbows and knees, followed by nails, hands, feet and trunk. Psoriatic arthritis is a less common form of psoriasis [2–4]. Three main clinical forms are distinguished, i.e. symmetrical polyarthritis, spondylitis and inflammation of one or more joints with accompanying muscular pain. Approximately 20–30% of patients with plaque psoriasis develop psoriatic arthritis. However, in about 10–15% of cases, psoriatic arthritis occurs before plaque psoriasis. Psoriasis also has a significant impact on patients’ quality of life. Currently, the severity of the disease assessment is based on determining the percentage of the body area involved, plaque location and thickness, presence of comorbidities, assessment of the patient’s physical and mental condition, and the burden of the pharmacotherapy used [2]. Many clinical scales have been developed to assess the disease severity, the most commonly used are Psoriasis Area and Severity Index (PASI), Dermatology Life Quality Index (DLQI), and Body Surface Area (BSA) [5]. Over the past decade, the perception of psoriasis, as a disease entity that includes only skin dysfunction, has
Inflammation and cardiovascular risk

Atherosclerotic plaque formation is induced by the accumulation of low density lipoproteins (LDL) within the artery wall. Oxidised LDLs (ox-LDL) serve as a signal to recruit monocytes, which differentiate to macrophages and convert them into foam cells [3, 9]. The endothelial activation causes overexpression of VCAM-1 and ICAM-1 cell adhesion molecules. In addition, ox-LDLs mobilise for the release of TNF-α, IL-1β, IL-6 and matrix metalloproteinases (Table 1). In the analysed atherosclerotic masses, the character of T-cell responses, in particular the Th1 subtype, was detected. Regulatory T-cells (Treg) play an important role in maintaining immune homeostasis by preventing autoimmunity. Loss of Treg cell number or a decrease in their response ability leads to atherosclerosis progression. The relationship between the increase in the incidence of cardiovascular events as well as the low level of Treg including the lack of the balance between Treg and T effector has been proven. In addition, positive effects of statins on the increase in the number of Treg lymphocytes were noticed. Experimental and clinical studies have proved the mutual influence of Treg on the metabolism of lipoproteins [12]. In turn, B-lymphocytes are responsible for the release of autoantibodies against oxidised forms of LDL. This action determines the formation of highly inflammatory deposits of immune complexes. In addition, B-lymphocytes present antigens to T-lymphocytes’ immunological memory, this promotes the secretion of cytokines and increases the concentration of costimulatory molecules. Ultimately, the consolidation of the presented mechanisms leads to the rebuilding of the atherosclerotic plaque with the accumulation of foam cells, collagen degradation, the erosion of the plaque and the weakening of the fibrous cap structure. The gradually arising unstable phenotype increases the risk of cardiovascular events. In summary, inflammation plays a key role in the progression and destabilisation of patients with atherosclerosis [9]. It is worth noting that individual biomarkers of inflammation, such as interleukin-6, C-reactive protein and metalloproteinases are considered independent prognostic predictors for the course of cardiovascular diseases (CVD) [13]. Currently, immunotherapy is an intensively analysed therapeutic solution dedicated to patients with advanced atherosclerotic lesions. However, due to the need for long-term use of modulation of the immune system, there is a risk of complications associated with immunosuppression. This limits the possibility of the therapy having widespread effects. Nowadays, vaccination-based methods are becoming a realistic therapeutic approach that can be implemented before the disease develops. Strategies that increase Treg, by restoring immune homeostasis, may be a beneficial solution in the treatment of atherosclerosis at various stages of myocardial disease. In addition, specific effector molecules of the immune system can be used as disease modifying agents by promoting the stabilisation of atherosclerotic plaque or improving lipid metabolism [9].

Inflammation, psoriasis and selected autoimmune diseases

The pathogenesis of psoriasis has not been fully explored. The causes of the disease are found in the disruption of complex interactions between keratinocytes, leukocytes as well as dendritic and epithelial cells [1, 3]. An abnormal immune profile in patients with exacerbated psoriasis contributes to the impairment of the inflam-
Table 1. Molecules connecting common pathways in atherosclerosis and psoriasis (based on [8, 10, 15, 17, 27])

**Membrane and other molecules**

| Membrane and other molecules | Function |
|------------------------------|----------|
| CD 14 Lipopolysaccharide receptor, monocyte differentiation antigen | Detects antigenic molecules |
| CD 29 Glycoprotein IIα, β1 integrin, β subunit of fibronectin receptor, β-chain in VLA (CD49) | Participates in inflammation, fibrosis and the apoptosis pathway |
| CD31 Platelet endothelial cell adhesion molecule | In combination with Annexin V+ is a risk factor for cardiovascular diseases |
| CD34 Hematopoietic antigen of progenitor cells | Participates in the attachment of hematopoietic stem cells to the extracellular matrix of the bone marrow or directly to stromal cells |
| CD45 Common leukocytic antigen (LCA), protein tyrosine phosphatase | Regulates the activation of T and B cells mediated by the antigen receptor |
| CD73 Ecto-5'-nucleotidase | Mediates co-stimulatory signals in the activation of T cells |
| CD90 Thy-1 | Presumably mediates the differentiation of hematopoietic stem cells and mediates the adhesion of white blood cells to activated endothelial cells |
| CD133 Prominin 1 or AC133 | Transmembrane glycoprotein undergoing expression on hematopoietic stem cells and progenitor endothelial cells |

**Antigen–receptor complex**

| Antigen–receptor complex | Function |
|--------------------------|----------|
| KDR Kinase insert domain receptor (a type III receptor tyrosine kinase) | Can interact with SHC-transforming protein 2, Annexin A5 and SHC-transforming protein 1 (important in the regulation of apoptosis) |
| VEGF Vascular endothelial growth factor | Two major pathways of endothelial tyrosine kinase signalling in angiogenesis |
| Tie 1, 2 Family of tyrosine kinases receptors | |

**Interleukins and their receptors**

| Interleukins and their receptors | Function |
|-------------------------------|----------|
| IL-1 (IL-1α, IL-1β) | Interleukin-1 type 1 receptor, Interleukin-1 type 2 receptor | Induces proinflammatory proteins, haematopoiesis, enables differentiation Th17 cells |
| IL-3(R) Interleukin-3 + receptor (CD131) | | Activates basophils and eosinophils, enables differentiation of dendritic and Langerhans cells |
| IL-6(R) Interleukin-6, R (sIL-6R), gp130 | | Enhances IL-2-induced proliferation and differentiation of B cells |
| IL-10(R) Interleukin-10, IL-10R1/IL-10R2 complex | | Immunosuppressive effect through antigen-presenting cells or direct effects on T-cell subsets |
| IL-12 Interleukin-12Rb1 and IL-12Rb2 | | Participates in development and maintenance of Th1 cells |
| IL-23 Interleukin-12b p40 5 40 kDa, Interleukin-23 p19 5 19 kDa | | Stimulates the production of proinflammatory IL17 |

**T helper cells**

| T helper cells | Function |
|----------------|----------|
| Th1 Type 1 T helper lymphocyte | Secretes γ-interferon, IL-2 and TNF-β, evokes cell-mediated immunity and phagocyte-dependent inflammation |
| Th17 Type 17 T helper lymphocyte | Multiple inflammatory processes, secretes IL-17A, IL-17F, IL-22, and IL-21 |

**Other mediators**

| Other mediators | Function |
|-----------------|----------|
| TNF-α Tumour necrosis factor α, cachexin | Induces tumour cell apoptosis and cachexia, development of the immune system, protection from pathogens, participates in autoimmune diseases |
| SCF Stem cell factor or kit ligand, mast cell growth factor | Promotes progenitor cell survival, accelerates stem cell entry into the cell cycle, chemotactic and chemokinetic factor for stem cells, anchor the hematopoietic cells in the microenvironment, induces progenitor cell adhesion to fibronectin |
Table 1. Cont.

| Membrane and other molecules | TGF-β | Vascular cell adhesion molecule 1, CD106 |
|-----------------------------|-------|----------------------------------------|
| G-CSF Granulocyte colony stimulating factor | | Mediates in adherence of inflammatory cells to target cells by binding with the β1-integrin ligand (very late antigen-4) on leukocytes |
| TGF-β Transforming growth factor β | | Cell adhesion |
| Platelet-derived growth factor (PDGF) | | |
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| Adhesion molecules | VCAM-1 Vascular cell adhesion molecule 1, CD106 | ICAM-1 Intercellular adhesion molecule 1, CD54 |
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Cardiovascular risk in patients with plaque psoriasis and psoriatic arthritis without a clinically overt cardiovascular disease: the role of endothelial progenitor cells

In the mortality attributed to myocardial infarction or stroke in this group of patients, The American Heart Association confirmed that mild and severe psoriasis are associated with an increased risk of myocardial infarction [24]. However recommendations for autoimmune disease by the European Society of Cardiology suggest use of a 1.5 risk multiplier for the CV risk in immune diseases like psoriasis in class IIb level C [25].

Cardiovascular risk assessment in people without clinically overt cardiovascular disease

People suffering from psoriasis, especially in its mild form, are often unaware of the systemic effects of chronic inflammation and the increased risk of CVD. Periodic assessment of the circulatory system determines the prognosis, thereby enabling implementation of early therapeutic steps. Basic check-ups include determination of the plasma lipid and glucose profile, diagnostics dedicated to the assessment of cardiac function (e.g. left ventricle ejection fraction, stroke volume left ventricle) and blood pressure measurement [9]. The tests showed that the platelet to lymphocyte ratio (PLR) value above the reference range is a predictor of total mortality and cardiovascular events. An increased number of platelets correspond to their increased activity, which can lead to a reduction in microcirculation flow. A relationship between a multiday hospital stay and the level of PLR was also observed. Namely, patients presenting increased PLR, showed a higher risk of adverse events than patients with ACS and lower PLR [26]. Molecular biomarkers associated with cardiovascular events and mortality due to CVD have become the subject of intensive research [13]. Results of this research have detected potential biomarkers from plasma measurement of cardiovascular disease and atherosclerosis progression, including those for (1) vascular endothelial growth factor (VEGF); (2) von Willebrand factor (vWF); (3) IL-6; (4) homocysteine and (5) tumour necrosis factor as a weak inducer of apoptosis (TWEAK) [13, 27–29]. The plasma C-reactive protein and N-terminal-pro-brain natriuretic peptide (NT-proBNP) can equally serve as an independent predictor of mortality caused by chronic heart failure [28, 29]. Additionally, CD31+/Annexin V+ EMP in relation to CD14+ CD309+ cells, added to the NT-proBNP score and clinical data provide a reliable value that distinguishes the kind of heart failure [11]. In conclusion, patients with psoriasis without clinically overt cardiovascular disease should have extended diagnostics performed for myocardial function and progression of atherosclerosis [30]. This information should be convincing for clinicians to start appropriate screening for CVD and oblige physicians to inform their patients about the need for periodic cardiovascular monitoring.

Laboratory methods

The key to understand what intercellular correlations lead to the development of CVD in patients with psoriasis is the mechanism of complex interactions between cells at the level of psoriatic and atherosclerotic plaque [3]. Determining the subtype of particles and the nature of their impact still requires further research. Currently, the assessment of inflammation with classic markers (CRP, leukocytes, ESR) provide insufficient information. Modern and progressively implemented prognostic methods which utilise biomarkers represent a great opportunity in reducing morbidity and mortality due to CVD [13]. This opens a direct route to cellular diagnostics. Stem cells are particles that demonstrate the ability to self-renew, differentiate and reprogram [31]. In situ hybridisation (ISH) technology allows the identification, characterisation and location of the stem cell population. In addition, the technique reveals markers for maintaining and regenerating stem cells. An important tool for advanced cellular diagnostics is flow cytometry analysis. It provides information on the expression of cell surface proteins by means of a reliable differentiation of positive and negative cells to a given antigen [32]. Other tools which are helpful in describing the particles include measurement of chromosomal content in cells by means of DNA cytometry or in situ fluorescence hybridisation [31]. Proteomic analysis, using two-dimensional electrophoresis and mass spectrometry, enables the determination of the protein profile in various pathological states. In addition, new cellular methods, based on progenitor cells, allow the regeneration of tissues damaged by the inflammatory process within them. Understanding the role of EPC in chronic inflammation brings hope to understanding the relationship between cardiovascular disease and autoimmune diseases [33]. EPC are circulating cells that have the ability to adhere to the endothelium at sites of hypoxia/ischaemia and participate in the formation of new vessels [34]. Tests performed on the EPC phenotype established CD34+, CD133+ as well as KDR expressions, however, the antigen panel may show a difference for hematopoietic and vascular endothelial subsets [11, 16, 33] (Table 1). Clinical trials were carried out on patients with heart disease, diabetes, peripheral arterial disease and cancer, in which the EPC served as a biomarker or had a beneficial regenerative effect. Perhaps, in the future, EPC will become a therapeutic tool in reducing mortality in general and mortality caused by CVD. The need for a thorough understanding of EPC participation in intercellular interactions may integrate common cardiovascular events with autoimmune diseases.

Conclusions

Patients with psoriasis, regardless of clinical manifestation or severity, are more likely to experience cardiovascular incidents in their lifetime. It is impossible to
precisely estimate the chances of CVD presenting itself. It is impossible to create objective risk stratification results, among others, from the presence of comorbidities and the difference in the age of onset of the first symptoms of psoriasis in the analysed group of subjects. There are high hopes that cellular diagnostics will abolish the existing correlation between cardiovascular diseases and autoimmune diseases [18–20]. Analysis of BMCS, progenitor EPCs and other biomarkers involved in the chronic inflammatory process shed new light on understanding the pathomechanism of both psoriasis and atherosclerosis [14–16]. However, the knowledge gained so far does not answer all the questions. Taking into account the role of angiogenesis in the recovery of ischemic tissue and the availability of the latest cellular diagnostic tools, we will most probably understand the increased risk of cardiovascular events in patients with psoriasis.

Conflict of interest

The authors declare no conflict of interest.

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