

Reducing cardiovascular burden in psoriasis patients by using specific therapies – How close are we?

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ABSTRACT

Psoriasis is a chronic, systemic inflammatory disease that has gained popularity among scientific research from many promising perspectives on diagnosis and treatment. Individuals with psoriasis associate numerous comorbidities and have many predisposing factors in common especially with heart disease. Based on this, researchers tried to identify the common pathogenic mechanisms, the impact of risk factors on both pathologies, the influence of one disease on the another as well as the impact of novel therapies used in psoriasis on cardiovascular system, in order to improve the prognosis and quality of life of these patients.

Areas of uncertainty. Pathogenic mechanisms involved both in psoriasis and atherosclerotic disease are not fully understood, especially in relationship with actual treatment strategies and their impact on prognosis. The purpose of this descriptive review is to summarize the latest available data, to see whether current treatment strategies of psoriatic disease should take into consideration the risk of cardiovascular disease (CVD) when one drug should be chosen at the expense of another.

Data sources. Literature research was performed using electronic database (PubMed, Cochrane Library and Web of Science) between January 2010 and June 2022. We used different keywords and MeSH terms to generate the most relevant results regarding psoriasis and cardiovascular disease. First, we evaluated the titles and abstracts of the articles and we excluded papers that didn't met selection criteria.

Keywords: psoriasis, cardiovascular disease, atherosclerosis, coronary artery disease, myocardial infarction, methotrexate, biologic therapy

INTRODUCTION

Psoriasis is a chronic, autoimmune disease determined by environmental and genetic factors for which there is no cure. Despite skin and nails or arthritic involvement, these patients are at higher risk of developing comorbidities, and cardiovascular disease (CVD) is no exception. Due to the difficulties in reporting this pathology, the incidence and prevalence show great variations depending on the region. The prevalence in studies vary from 0.09% to 11.4% [1] making psoriasis a serious global health

problem with at least 100 million people diagnosed worldwide [2].

It is an underdiagnosed and undertreated disorder. Although skin damage is the most obvious and can be recognized as the only manifestation of the disease, its recognition as a multisystemic disease is really necessary to improve diagnostic and therapeutic approach [3].

Increasing evidence supports the fact that psoriasis should be considered a multisystem chronic inflammatory entity with associated comorbidities. The link between psoriasis and other patholo-

gies is today attributed to a proinflammatory state and many other mechanisms. Multiple epidemiologic studies suggest an association between metabolic syndrome or components of it and psoriatic disease [4–6]. Metabolic syndrome is in turn one of the main pillars of increased cardiovascular (CV) risk and small studies show possible benefits following the treatment of metabolic syndrome [7].

The more severe the psoriatic disease, the more important the CV risk profile. Some of the pathophysiological mechanisms responsible for this correlation are: similar inflammatory pathways, impaired angiogenesis and endothelial dysfunction [8]. Ongoing inflammation strongly influences the incidence of CV events as demonstrated by Gelfand et al. in a prospective, population-based cohort study in the United Kingdom [9] but the consideration of psoriasis as an independent risk factor for the occurrence of cardiovascular disease (CVD) is a topic of interest to researchers.

Compared to healthy controls, traditional risk factors for CVD, such as: hypertension, diabetes, obesity, dyslipidemia, smoking and excessive alcohol consumption, occur more often in patients with psoriasis [10]. Full understanding of mechanisms by which CVD develops in patients with autoimmune disorders could be a huge step in implementing targeted cell therapy in order to improve patients' quality of life (QoL).

We aimed in this descriptive review to gather the latest available data regarding psoriasis and its link to heart disease to outline an overview of treatment strategies and their impact on cardiovascular system.

PSORIASIS AS A CARDIOVASCULAR RISK FACTOR

In the European guidelines on CVD prevention, inflammatory conditions, such as psoriasis, are considered risk factors for development of CVD. Despite weak evidence for psoriasis compared to rheumatoid arthritis, it seems rational to consider the existence of this disease when initiating preventing interventions [11]. Similarly, in a report of the American College of Cardiology/American Heart Association (ACC/AHA) in management of blood cholesterol guideline we also find psoriasis being considered a risk-enhancing factor for CVD [12].

Uncertainty about whether CVD risk can be directly attributed to psoriatic disease, led researchers to investigate this issue. In a systematic review and meta-analysis conducted by Samarsekera et al [13] the results showed that there is a link that necessitates further long-term, large-scale cohort studies to focus on confounding factors and bias identification in order to see whether aggressive treatment strategies in severe forms has an impact in CVD end points.

ATHEROSCLEROTIC DISEASE

Atherosclerotic disease includes cardiovascular, cerebrovascular and peripheral vascular disease. Atherogenesis is a dynamic, immune-driven process, leading to endothelial dysfunction [14] with hyperlipidemia and inflammation being the pillars of atherosclerosis development [15]. Patients with psoriasis pose an elevated risk for atherosclerosis. The exact mechanisms of this association is not fully understood, but it most likely involves humoral and cellular inflammatory mediators [16]. Although these patients have comorbidities such as hypertension, diabetes, and obesity, comorbidities that predispose to atherosclerotic heart disease, after adjustment for them, patients still maintain an increased CV risk [17].

Patients with psoriatic arthritis (PsA) tend to have a higher prevalence of subclinical atherosclerosis [18]. The association between psoriasis and carotid intima-media thickness (CIMT) was evaluated in a meta-analysis and showed that psoriatic patients had a significantly thicker CIMT than controls supporting the idea of subclinical atherosclerosis in many patients with psoriasis [19].

CORONARY ARTERY DISEASE

Coronary computed tomography (CCTA) today allows the characterization of atheroma plaques on the basis of which the atherothrombotic risk can be established. Recently, Yamazaki et al performed CCTA in patients with psoriasis and found that prevalence of CV lesions is significantly higher than that in healthy controls [20].

Mansouri et al compared coronary artery calcification in patients with moderate to severe psoriatic disease with that of diabetic patients without psoriasis [21]. The findings of their study are promising, showing that both groups had same calcification risk but 3 times higher than controls (healthy patients). Particularly, the calcification risk was irrespective of body mass index (BMI) in psoriatic patients, comparative to diabetic subgroup where BMI and calcification risk were correlated.

Psoriatic patients represent a vulnerable population. One study tried to evaluate total and non-calcified coronary plaque burden (NCB) and high-risk plaque (HRP) prevalence, between patients with psoriasis and patients with hyperlipidemia and demonstrated that psoriasis patients group had greater NCB and increased HRP prevalence compared to the healthy individuals [22]. Also, when compared to older hyperlipidemic patients, psoriasis patients have elevated NCB and same HRP prevalence.

MYOCARDIAL INFARCTION

The association between psoriasis and myocardial infarction (MI) is an intensely researched and debated topic. Some studies, but not all, show a strong relationship between them.

A study conducted by Egeberg et al. investigated the risk of MI in patients with psoriasis and psoriatic arthritis (PsA) and showed only a slightly increase in the risk of MI in patients with severe psoriasis (HR 1.21; 1.07-1.37). Though some papers report an increased CV mortality in hospitalized individuals with severe forms compared with the general population, in outpatients with psoriatic disease no higher risk was found [23].

Regarding the characteristic of “independent risk factor” of psoriasis for CVD, so far there are inconclusive data. According to a meta-analysis, the risk of MI could be 2-times higher in patients with severe psoriatic disease [24] but other papers report different outcomes. For example, Gelfand et al. conducted a prospective, population-based cohort study in the United Kingdom (UK) to see if psoriasis is an independent risk factor for MI when controlling for major cardiovascular risk factors. Their results suggest that psoriasis could be an independent risk factor, with the highest risk in young patients with severe psoriatic disease and is attenuated with age but remains increased after adjusting for traditional risk factors [9].

Karbach et al used a nationwide German inpatient sample to compare patients with MI with and without psoriasis and analyzed the impact of psoriasis on the outcome of hospitalized patients for acute MI. Their findings were that psoriasis increases cardiovascular risk and may be the cause of MI at younger ages, but in-hospital mortality rate in patients with MI and psoriasis was lower, possibly due to young age [25].

On the other side, opposite results had been found in another paper using overlapping cohorts. They failed to prove an independent connection between CVD risk and psoriasis [26] mainly because of the study design and a short term follow-up. However, gathering most recent data, results are sparse and inconsistent [25].

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

Individuals diagnosed with psoriasis may also have an enhanced risk of major adverse cardiovascular events (MACE) beyond that of traditional CV risk factors. Several studies have found higher rates of CV mortality, MI, and stroke [27,28] in psoriatic patients.

Ogdie et al quantified the risk of MACE in a population-based longitudinal cohort study among patients with PsA, rheumatoid arthritis (RA), and psoriasis

without known PsA comparative to general population. Using data from The Health Improvement Network (THIN) in UK. After adjusting traditional risk factors, they found that the risk of MACE was higher in all subgroups, and highest in patients with PsA not taking DMARDs as compared to controls [28]. The conclusion of a systematic review and meta-analysis of observational studies was that both mild and severe forms of psoriasis are linked to an enhanced risk of MI and stroke and severe forms have a higher risk of CV mortality [29].

PATHOPHYSIOLOGICAL LINK BETWEEN PSORIASIS AND ATHEROSCLEROSIS

Neutrophils and inflammation

Involvement of neutrophils in common pathogenic mechanisms for psoriasis and atherosclerotic disease has drawn attention to researchers. Neutrophils are the first cells to be recruited at the site of inflammation and are the main regulators between the innate and adaptive immune system [30]. They are involved in the onset of atherosclerosis in early phases by promoting the accumulation of monocytes, macrophages, and low-density lipoprotein cholesterol (LDL-c) in the subintimal layer, and in the late stages by contributing to plaque destabilization [31]. The neutrophil to lymphocyte ratio (NLR) is a biomarker used as a predictor of CVD and all-cause mortality that can also be used in patients with psoriasis. NLR may be used as a biomarker of subclinical CVD in patients with psoriatic disease, as showed in a study conducted by Kvist-Hansen et al [30], where they found that those patients had an increased expression of genes related to neutrophil degranulation compared to psoriasis patients without CVD. Another study also proved a positive association between NLR and vascular inflammation in the carotid arteries, in patients with psoriasis and CVD [32].

One of the main pillars of the pathogenesis of psoriasis is linked to the interleukin 23/T-helper 17 pathway. Targeted anti IL-17 therapies have proved efficacy in moderate to severe plaque psoriasis [33]. Similarities between psoriasis and atherosclerosis through IL-17 and neutrophils require further studies to elucidate this relationship [14].

Angiogenesis and oxidative stress

Pathologic angiogenesis is described in inflammatory diseases such as psoriasis or rheumatoid arthritis (RA). During the pathogenesis of both atherosclerosis and psoriasis, local injury or local hypoxia trigger the release of IL-8, HIF-1 α , ETS-1, and vascular endothelial growth factor (VEGF), factors known to be proangiogenic [34]. Also, oxidative and angio-

genic pathways share common pathways in both disorders. Common mechanisms involve enhanced production of reactive oxygen species (ROS). Targeting these pathogenic pathways could provide a better CV prognosis for these patients.

Endothelial dysfunction

Endothelial dysfunction is one of the key mechanisms implied in atherosclerosis development. Several factors, such as proinflammatory cytokines, ROS, oxidized LDL-c and CV risk factors, activate endothelial cells and alter their normal function. All the factors mentioned above, are also altered in psoriatic disease. A study conducted by Haberka et al aimed to assess selected serum biomarkers and vascular indices of CV risk in patients with mild to moderate psoriatic disease. The main finding was that there is an association between mild to moderate psoriatic disease and increased oxidative stress, endothelial dysfunction, adipokine imbalance and accelerated subclinical atherosclerosis [35].

Common inflammatory biomarkers

Classical biomarkers of inflammation show high values compared to the healthy population in both CVD and psoriasis patients. Therefore, there are high chances that cardiovascular risk will not be estimated correctly. In many situations, young patients with psoriatic disease have a low Framingham risk score, but they still pose a high CV risk [36].

High-sensitivity C-reactive protein (hs-CRP) is extensively studied as an inflammatory marker in various diseases and it has been found to have a strong association with subclinical atherosclerotic disease [37], therefore, considered to be used as a predictive factor for CV events. However, it has been shown to be a nonspecific marker [38]. When talking about psoriatic disease, to date, there are inconsistent data regarding positive correlations between disease severity and hs-CRP [39,40].

A novel spectroscopic biomarker, GlycA, could serve as a useful clinical marker for systemic inflammation. It's characterized by low intra-individual variability and other attributes making it a very promising marker in patients with chronic inflammatory and autoimmune disorders [41]. Some studies have proved GlycA to be a good predictor of future CV events [42,43]. A recent two-stage study conducted by Joshi et al evaluated the link between subclinical CVD in psoriasis and GlycA levels [44]. Their results provided strong evidence for an association between psoriasis and GlycA and also between subclinical CVD in psoriasis and GlycA. Given these findings, a potential role of GlycA in evaluating inflammatory state in patients with CV risk and psoriasis could be superior to hs-CRP levels for

which further studies are needed to confirm these findings.

CONSEQUENCES OF PSORIASIS TREATMENT TO CARDIOVASCULAR SYSTEM

Non-biologic therapeutic agents

Patients with psoriasis are known to have dysregulation of inflammatory and lipid metabolism genes that have been proved to be linked to atherosclerotic CVD. Certain medications increase the risk of CVD while other systemic therapies reduce the risk of CVD. From the approved non-biologic therapies, Methotrexate (MTX) has been linked with favorable cardiovascular effects, while Acitretin, Cyclosporine and Apremilast either had no effect or had a negative effect on CVD [45].

According to latest data, among non-biological psoriatic treatments, only MTX shows beneficial effects on CV system. One of the first studies that evaluated the effect of MTX therapy on the incidence of vascular disease in patients with rheumatoid arthritis (RA) and psoriasis, demonstrated that MTX therapy reduces the incidence of vascular disease and was thought to be related to the anti-inflammatory effect of MTX [46].

A recent small prospective randomized comparative study tried to assess the impact of vitamin D in association with MTX in psoriasis treatment and found that the use of MTX may decrease CVD risk factors. They observed improvements in carotid intima-media thickness (CIMT) and blood pressure (BP) but no significant decrease in hs-CRP levels [47].

BIOLOGIC THERAPEUTIC AGENTS

Tumor necrosis factor- α antagonists

Tumor necrosis factor- α (TNF- α) inhibitors have a positive impact on the clinical symptoms of PsA and also slows structural damage of joints [48]. A very good response was demonstrated for etanercept by Mease et al [49] in several studies. Also, infliximab, adalimumab, golimumab, certolizumab showed similar beneficial effects [50].

A randomized study of a small group of patients with moderate to severe psoriatic disease and a history of coronary atherosclerosis sought to evaluate the effects of adalimumab on the degree of vascular inflammation. Vascular inflammation was measured in the carotid artery and ascending aorta, by 18F-fluorodeoxyglucose uptake on positron emission tomography. Although the study did not reach the primary endpoint, conclusion was that adalimumab may reduce vascular inflammation in these patients but their results were not significant in this small sample size [51].

Two molecules expressed in the endothelium, vascular cell adhesion molecule 1 (VCAM-1) and E-selectin have been studied by Zdanowska et al [52] to assess atherosclerosis severity in patients with plaque psoriasis, patients treated with MTX or Adalimumab and compared with controls. The results indicated a correlation between systemic therapy and E-selectin and VCAM-1 levels, which could be associated with the risk of CVD development. However, treatment with Adalimumab showed a significant decrease only in VCAM-1 plasma concentrations.

In a systematic literature review written by Roubille et al, it was shown that TNF- α inhibitors are associated with a lower risk of CV events while corticotherapy and non-steroidal anti-inflammatory drugs (NSAIDs) are associated with an increased risk in patients with RA, but limited evidence exists for patients with psoriasis or PsA regarding CV effects [51]. According to their selection criteria, they had enough studies just to evaluate the effect of systemic therapy versus topical treatment or no systemic treatment on risk of CV events. Although these data showed a significant reduction in CV events, it should be noted that the evidence is less conclusive than that for RA.

OTHER BIOLOGIC TREATMENTS

Ustekinumab, a monoclonal antibody that inhibits IL 12 and IL 23, represents a novel therapeutic agent for psoriasis due to the effects on the immune system [53]. It has systemic effects that can be beneficial in selected patients with psoriatic disease and certain comorbidities. However, studies show conflicting data. A meta-analysis showed no change in the risk of MACE when compared to placebo [54] but in a randomized clinical trial results indicated that there may be an improvement in myocardial function in psoriatic patients [55]. Also, in other meta-analyses, there were conflicting results, suggesting that other prospective, well-controlled studies are needed [54,56].

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The other monoclonal antibodies, known as IL-17 and IL 23-23 inhibitors (Secukinumab, Ixekizumab, Brodalumab, Guselkumab) showed in majority of studies no change in risk of MACE [45,54,57,58]. Immunotherapy is still analyzed as a therapeutic option for patients with advanced atherosclerotic lesions.

DISCUSSIONS AND CONCLUSION

Severe forms of psoriatic disease are often treated with anti-inflammatory biologic therapies. Due to the strong association between severe inflammation caused by psoriasis and the CV risk attributed to chronic inflammation, more and more hypotheses related to the effects of biological treatments on CV risk were tested with favorable results. In an observational, prospective study, was proved that biologic therapy in severe forms is associated with favorable modulation of coronary plaque indices measured by CCTA [59]. "Psoriasis severity is related to the burden of coronary disease – our findings suggest treating the psoriasis may potentially benefit coronary heart disease." said the author of the study, Dr Nehal Mehta.

With each new study, the evidence for the beneficial effect of biologic therapy becomes stronger. However, of the wide range of biologic treatment options, not all have shown the same effect on the CV system and the comparison of various biological therapies is imperative in further studies.

Treating psoriasis is a proficient way of reducing the risk of MACE. Perhaps a specific selection of therapy in patients with psoriasis, appropriate to the degree of CV risk, will allow better outcomes in these patients. We suggest that large, prospective, controlled and powered studies to compare CV outcome in patients with psoriasis and different treatment regimens would be useful for a better understanding of the positive and negative impact that new therapies bring in patients with mild to severe forms of psoriasis on CV morbidity and mortality.

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