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REVIEW

Psoriasis and Cardiovascular Risk: A Comprehensive Review

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ABSTRACT

Psoriasis is a systemic inflammatory disorder that involves complex pathogenic interactions between the innate and adaptive immune systems. Individuals with psoriasis have an increased risk of developing other chronic health diseases such cardiovascular disorders. The high incidence of cardiovascular events in the population with psoriasis could be explained by several mechanisms. The high prevalence of traditional cardiovascular risk factors and metabolic abnormalities contributes to the high cardiovascular burden in patients with psoriasis. Likewise, the presence of systemic inflammation in combination with metabolic abnormalities may act in a synergistic manner to increase cardiovascular risk in these patients. This review focused on epidemiologic and clinical evidence linking psoriasis to cardiovascular risk factors and cardiovascular disease. We described the possible pathophysiological mechanisms that justify this association and analyzed the best way to stratify the cardiovascular risk in patients with psoriasis. We also described the usefulness of the therapies frequently used in cardiovascular prevention and analyzed the impact of the specific psoriasis medication on cardiovascular risk factors or major atherosclerotic events. Knowledge of the application of different cardiovascular prevention strategies could mean an advantage in performing the difficult task of estimating cardiovascular risk and treating cardiovascular risk factors in this particular group of patients.

Keywords: Cardiovascular disease; Cardiovascular risk factors; Cardiovascular risk stratification; Psoriasis; Statins

Key Summary Points

Psoriasis is a chronic inflammatory skin disease associated with increased cardiovascular morbidity and mortality.

Patients with psoriasis have an increased prevalence of classic cardiovascular risk factors, but psoriasis may provide an additional and independent cardiovascular risk factor: inflammation.

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INTRODUCTION

Psoriasis is a systemic inflammatory disorder that involves complex pathogenic interactions between the innate and adaptive immune systems, affecting approximately 2% of the population [1].

Several important diseases occur more often in patients with psoriasis than expected based on their respective prevalence in the general population. Individuals with psoriasis have an increased risk of developing other chronic health diseases such as psoriatic arthritis, metabolic syndrome (MetS), depression, non-alcoholic fatty liver disease, Crohn's disease, lymphoma and cardiovascular disorders [2].

The relationship between psoriasis and an increased incidence of major adverse cardiovascular events has been observed in multiple epidemiologic studies. McDonald and Calabresi first demonstrated that the risk associated with vascular diseases was 2.2 times higher in more of 300 hospitalized patients with psoriasis than in controls with other dermatologic conditions [3, 4].

The higher incidence of cardiovascular events in the population with psoriasis could be explained by several mechanisms. The high prevalence of traditional cardiovascular risk factors and metabolic abnormalities contributes to the high cardiovascular burden in patients with psoriasis. Likewise, the presence of systemic inflammation in combination with metabolic abnormalities may act in a synergistic manner to increase cardiovascular risk in these patients [5].

This review focused on epidemiologic and clinical evidence linking psoriasis to cardiovascular risk factors and cardiovascular disease. We described the possible pathophysiologic mechanisms that justify this association and analyzed the best way to stratify the cardiovascular risk in patients with psoriasis (clinical scores, imaging techniques used to assess subclinical atherosclerosis). We also described the usefulness of the therapies frequently used in cardiovascular prevention (aspirin, lipid-lowering drugs, antihypertensive therapy, hypoglycemic agents) and analyzed the impact of the specific medication of the psoriasis on cardiovascular risk factors or major atherosclerotic events.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

ASSOCIATION BETWEEN PSORIASIS AND CARDIOVASCULAR RISK FACTORS

Smoking

Smoking is associated with an increased risk of cardiovascular disease, and prior studies have suggested that patients with psoriasis are more likely to be active smokers. Moreover, smoking is a possible risk factor for the onset of psoriasis, although the evidence remains limited and contradictory [6–8].

A previously published meta-analysis determined that that smoking is an independent risk factor for the development of psoriasis and that patients with established psoriasis continue to smoke more than patients without psoriasis [9]. Another meta-analysis showed not only a positive association between the presence of psoriasis and the prevalence of smoking, but also between tobacco and the severity of psoriasis [10].

Several pathophysiologic mechanisms may explain the association of smoking with psoriasis [11–13]. The nicotinic acetylcholine receptors are found not only in the nervous system and adrenal medulla, but have also been identified in other tissues, such as skin keratinocytes and inflammatory cells. Smoking causes oxidative stress and production of dangerous free radicals, interfering with signal pathways relevant in psoriasis such as mitogen-activated protein kinase, nuclear factor kappa B and JAK-STAT pathways. Nicotine also induces an increased secretion of several cytokines such as interleukin (IL)-12, tumor necrosis factor (TNF), IL-2 and granulocyte-monocyte colony-stimulating factor, which play a crucial role in the pathogenesis of psoriasis [14]. The action of nicotine on the skin and inflammatory cells

could facilitate keratinocyte adhesion and upward migration in the epidermis and may have an immunomodulatory effect, interfering with immune cell signaling [15].

Finally, tobacco could negatively influence the response to treatment. In that sense, an observational study showed that heavy smoking could decrease the treatment effect of anti-TNF drugs in patients with psoriatic arthritis [16]. Similarly, a small retrospective study showed that current smoking at the start of anti-TNF therapy was associated with non-response to TNF blockers [17].

Obesity and MetS

MetS consists of a group of metabolic risk factors including central obesity, glucose intolerance, hypertension, hypertriglyceridemia, low levels of high-density lipoprotein (HDL) and insulin resistance. The MetS is associated with a twofold increase in cardiovascular outcomes and a 1.5-fold increase in all-cause mortality [18].

The association between psoriasis and obesity has been largely supported by evidence. In Argentina, a cross-sectional study (1286 psoriasis patients and 2547 controls) showed that the prevalences of overweight (43% vs. 40%, $p < 0.01$) and obesity (30% vs. 24%, $p < 0.01$) were higher in the psoriasis group compared with controls [19]. In a Danish study, more adolescents with mild psoriasis were obese (8.6% vs. 1.7%, $p = 0.008$), and physical measures of abdominal obesity were also significantly higher compared with the control group [20].

On the other hand, some authors described that the risk of psoriasis being increased in the obese population, and this clinical scenario may negatively affect systemic treatment of psoriasis [21].

A recent meta-analysis (63 studies encompassing 15,939 psoriasis patients and 103,984 controls) showed that 30.3% of psoriasis patients were reported with MetS compared with 21.7% subjects in the control group [OR 2.18 (95% CI 1.84–2.34)] [22]. Similarly, another meta-analysis showed that the association between psoriasis and MetS is high in Latin America [23].

As with obesity, in a large prospective study from a general population, the presence of MetS was associated with increased risk of incident psoriasis, and the authors suggest that this positive association could, at least partly, be attributed to adiposity [24].

Consequently, the relationship between MetS and psoriasis is bidirectional, where inflammation is the common pathophysiologic substrate between both entities. In that sense, growing knowledge suggests that the Th17 cells and IL-23 may be a link between cutaneous and metabolic manifestations of psoriasis [25].

Hypertension

Data from epidemiologic studies show that hypertension is more prevalent among psoriasis patients, and prevalence is associated with psoriasis severity [19, 26–28]. A recently published meta-analysis demonstrates that psoriasis is associated with an increased risk of hypertension compared with those without psoriasis [29].

Additionally, psoriasis patients are prone to suffer difficult-to-control hypertension. A case-control study showed that, compared with hypertensive patients without psoriasis, psoriasis patients with hypertension were five times more likely to be on a monotherapy antihypertensive regimen, 9.5 times more likely to be on dual antihypertensive therapy and 16.5 times more likely to be on a triple antihypertensive regimen after adjusting for traditional cardiac risk factors [30].

As previously described for other risk factors, hypertension was significantly associated with an increased risk of psoriasis incidence [31].

Again, it is accepted that inflammation underlies the pathogenesis of hypertension, and activated immune cells are critical factors within this process [32, 33].

Dyslipidemia

"Atherogenic dyslipidemia" is associated with increased cardiovascular risk [34]. Its main

findings include hypertriglyceridemia, low HDL cholesterol levels, qualitative changes in low-density lipoprotein (LDL) particles (size reduction, increase in density, oxidation), accumulation of remnant lipoproteins and postprandial hyperlipidemia. Small LDL particles can accumulate in the tunica intima to initiate atherosclerosis. These LDL particles undergo oxidative modification producing oxidized LDL (oxLDL) that may enter macrophages to get transformed into foam cells, leading to the development of atherosclerotic plaques. Products of oxLDL may injure vascular wall cells to produce cytokines and inflammatory mediators, thereby promoting low-grade inflammation and progression of atherosclerotic plaques.

Psoriasis is associated with an atherogenic lipid profile and significant lipid abnormalities have been noted even during 5 years preceding onset of psoriasis [35]. Similarly, another study reported that the mean oxLDL levels in patients with psoriasis were significantly higher than those of healthy controls [36].

On the other hand, HDL is involved in reverse cholesterol transport, inhibition of monocytic infiltration and thus suppression of atherogenicity. In patients with psoriasis, not only lipoprotein levels can be altered, but also their composition and function may be significantly different from controls. This is an important observation because the composition and function of HDL are actually considered more important than the quantity of HDL itself. In that sense, Mehta et al. showed that the HDL efflux capacity in psoriasis patients compared with controls was diminished beyond cardiovascular risk factors [37].

The plasma concentration of the major apoprotein of LDL cholesterol, apolipoprotein B, is associated with the development of atherosclerosis and higher cardiovascular risk. Also, lipoprotein (a), a genetic variant of LDL with apolipoprotein B linked to apolipoprotein-a by a disulfide bond, is also susceptible to lipid peroxidation and is said to have both thrombogenic and atherogenic roles. A recently published meta-analysis showed that lipoprotein (a) and apolipoprotein B levels were significantly higher in patients with psoriasis compared with controls [38].

Importantly, all lipid abnormalities observed in the patient with psoriasis have systemic inflammation and insulin resistance as a substrate. Consequently, the association with other risk factors such as obesity and MetS is strong.

Diabetes

A systematic review reported that the average prevalence of type 2 diabetes in psoriasis patients was 11.6% (15 epidemiologic cohorts evaluated) [39]. The same study showed an increased prevalence of type 2 diabetes in subjects with psoriasis compared with controls (11 studies evaluated). The mean type 2 diabetes prevalence was 10.3% in psoriasis patients and 6.2% in controls. The heterogeneous findings complicate a reliable estimate of the true prevalence of diabetes in patients with psoriasis but the prevalence of diabetes observed in the psoriasis patients was systematically higher than in the healthy population.

However, many new cases of diabetes have been reported in the population with psoriasis compared with subjects without the disease. In a study of 108,132 patients with psoriasis, the adjusted hazard ratios for incident type 2 diabetes were 1.11 (95% CI 1.07–1.15) in the mild psoriasis group and 1.46 (1.30–1.65) in the severe psoriasis group [40]. Similarly, a meta-analysis (eight cohort studies included) reported a relative risk of 1.50 (95% CI 1.27–1.77) for diabetes incidence in patients with psoriasis [41].

The relationship between psoriasis and diabetes can be partially explained by the increase in obesity and unhealthy lifestyles and possibly can be related to insulin resistance associated with inflammation. However, other mechanisms have been proposed to explain this association. Genetically, several genes (CDKAL1, PTPN22, ST6GAL1, JAZF1) have been linked to both type 2 diabetes and psoriasis [42, 43]. Additional emerging pathways that are implicated include those of the glucagon-like peptide-1 receptor and the incretin effect [44, 45].

However, at present, the exact mechanistic links between the two diseases are not entirely understood and warrant further investigations.

Physical Activity

While numerous studies have suggested an association between psoriasis and physical activity, others have yielded contradictory results.

A recently published meta-analysis combined data of 13 studies including a total of 149,499 participants [46]. There was no significant difference in the level of exercise between people without and with psoriasis when analyzed for the overall effect but the subgroup analysis showed that patients with psoriasis performed vigorous exercises significantly less than controls (RR 0.76; 95% CI 0.67–0.85; $p < 0.00001$). Also, patients with a higher proportion of psoriatic lesions and self-awareness were associated with lower intensity exercises.

Similarly, another systematic review showed that individuals with psoriasis are less likely to participate in vigorous physical activity compared with individuals without psoriasis [47].

In a large cohort of women in the USA, the association between physical activity and incident psoriasis was evaluated (1026 incident psoriasis cases during 1,195,703 person-years of follow-up) [48]. In this study, vigorous physical activity was independently associated with a reduced risk of incident psoriasis [multivariate RR for the highest quintile, 0.66 (95% CI 0.54–0.81; $p < 0.001$)]. The mechanism whereby physical activity reduces psoriasis risk deserves further study. It is biologically plausible that physical activity may affect psoriasis risk through effects on systemic inflammatory mediators.

Association Between Psoriasis and Cardiovascular Events

An estimated prevalence of cardiovascular heart disease of 14.3% has been observed in North American patients with psoriasis, which is higher (11.3%) than that of the general population [49]. A cross-sectional study developed in Argentina showed that regardless of age and the presence or absence of diabetes, hypertension or smoking, there was a significant association between coronary artery disease and psoriasis (OR 1.48, 95% CI 1.04–2.11, $p = 0.03$) [19].

Likewise, a prospective, population-based cohort study of patients with psoriasis in the UK showed that the incidences of myocardial infarction per 1000 person-years for control patients and patients with mild and severe psoriasis were 3.58 (95% CI 3.52–3.65), 4.04 (95% CI 3.88–4.21) and 5.13 (95% CI 4.22–6.17), respectively. The relative risk was greatest in young patients with severe psoriasis [50].

Furthermore, patients with psoriasis, particularly if severe, have an increased risk of stroke that is not explained by major stroke risk factors identified in routine medical care [51, 52].

Additionally, a retrospective cohort of patients with psoriasis showed higher mortality rates during follow-up compared with the control group [53]. In the same way, another study showed that patients with severe psoriasis have an increased risk of cardiovascular mortality that is independent of traditional cardiovascular risk factors [54].

Finally, Pietrzak et al. developed a meta-analysis that indicates an elevated risk of cardiovascular events in psoriatic patients in relation to non-psoriatic controls (OR 1.28; 95% CI 1.18–1.38) [55]. In another recently published meta-analysis, Saumya et al. obtained results supporting a significant association between psoriasis and incidence of major adverse cardiovascular events. The incidence of cardiovascular events among psoriasis patients was dominant in the Middle East population compared with other geographic locations considered in this study. The differences found may be related to variations in genetic structure, environmental exposures or issues related to healthcare use [56].

Pathogenetic mechanisms of cardiovascular disease in psoriasis patients appear to be of a complex nature. The development of atherosclerosis and its increased prevalence may be partially explained by the presence of atherosclerotic risk factors as well as by the chronic inflammatory processes that are commonly observed in psoriasis. Previous studies have established psoriasis primarily as a T cell-mediated disorder. While initial evidence

implicated a predominant role of helper T cells type 1 (Th1), recent research shows the importance of the Th17 and other IL-17 producing cell types [57]. All the subtypes of T cells involved in the pathogenesis of psoriasis are also involved in atherosclerosis [58]. Therefore, the main hypothesis is that the chronic inflammation that occurs in psoriasis is more than skin deep and results in multiple systemic mechanisms that are shared with other chronic inflammatory diseases, including atherosclerosis. In addition, Flammer and Ruschitzka proposed the theory of "two plaques for one syndrome" since molecular mechanisms as well as the pro-inflammatory cytokine profile of psoriatic lesions are remarkably similar to those of atherosclerotic ones, with a comparable inflammatory infiltrate of T cells, macrophages and monocytes [59].

STRATIFICATION OF CARDIOVASCULAR RISK

Clinical Scores

The estimation of cardiovascular risk with traditional scores has great limitations. On the one hand, these predictive tools were not specifically developed in patients with psoriasis. On the other, the performance of these scores is suboptimal because traditional cardiovascular risk factors do not fully explain the increased cardiovascular risk in patients with psoriasis, and current risk functions do not represent other contributing factors. Consequently, cardiovascular risk is often underestimated.

One study has found that the Framingham score has a limited ability to correctly stratify patients with psoriasis [60]. The majority of patients in the intermediate risk group based on that score and almost half of the patients in the low-risk group were reclassified in a higher risk group after a carotid ultrasound evaluation. The underestimation of risk was higher in subjects with psoriatic arthritis. Another study that evaluated several risk scores classified the majority of psoriasis patients as "low risk" [61].

Gisondi et al. showed that the Framingham risk score was significantly higher in patients with psoriasis than in controls at 5 years (mean ± SD 5.3 ± 4.4 vs. 3.4 ± 3.3, $p < 0.001$) and at 10 years (11.2 ± 8.1 vs. 7.3 ± 6.3, $p < 0.001$) [62]. Indeed, another study showed that a high percentage of patients at low or intermediate cardiovascular risk according to the Framingham score must be reclassified as intermediate and high risk, respectively, when psoriasis is added as a scoring factor [63].

To address these limitations, some recommendations for cardiovascular risk management proposed to apply a 1.5 multiplier to any calculated cardiovascular risk score to accommodate the risk [64, 65]. Another way to optimize risk stratification is to add another predictive factor, such as the detection of subclinical atheromatosis.

Imaging Techniques Used to Assess Subclinical Atherosclerosis

Indicators of early vascular atherosclerosis such as carotid mid-intimal thickness, pulse wave velocity, endothelial function and coronary calcium score quantified by computed tomography are frequently altered in patients with autoimmune diseases in general and psoriasis in particular [66–70]. The presence of carotid atherosclerotic plaques has also been observed commonly in subjects with psoriasis and psoriatic arthritis [71, 72]. Moreover, the burden of carotid atherosclerosis quantified by ultrasound is associated with an increased risk of developing future cardiovascular events [73].

However, a coronary calcium score > 400 was more frequently observed in patients with severe psoriasis, even adjusting for the risk estimated by the Framingham score [74]. Recently, a systematic review and meta-analysis showed that the patients with psoriasis had an increased risk of coronary calcium score > 0 (RR 1.14, 95% CI 1.04–1.26; $p = 0.004$) and > 100 (RR 1.71, 95% CI 1.28–2.30; $p < 0.001$) compared with controls [75].

A recent Argentine Consensus suggests that it would be reasonable to consider the search for subclinical carotid atheromatosis by ultrasound or to calculate the coronary calcium score by computed tomography to achieve accurate

Table 1 Limitations and recommendations related to cardiovascular risk stratification in patients with psoriasis

Stratification of cardiovascular risk	
Problems and limitations	The clinical scores were not specifically developed in patients with psoriasis
	The performance of clinical scores is suboptimal because the scores do not include non-traditional risk factors such as inflammation
	Cardiovascular risk is frequently underestimated
Proposals to optimize the evaluation	It is recommended to use the risk scores for the initial stratification of cardiovascular risk in patients with psoriasis by adjusting the result by a multiplier factor of 1.5
	It would be reasonable to consider the search for subclinical carotid atheromatosis by ultrasound or to calculate the coronary calcium score by computed tomography as part of the stratification of cardiovascular risk, particularly in subjects characterized with intermediate risk by risk scores
	In patients with psoriasis stratified as low risk, a cardiovascular evaluation would be appropriate at least every 3 years. At intermediate risk, the evaluation should be annual. Patients classified as high risk require intensive preventive interventions, without the need for a new evaluation

stratification of cardiovascular risk in patients with psoriasis, particularly in subjects characterized with intermediate risk by risk scores (class IIa, level B) [76].

The current problem to correctly stratify cardiovascular risk in patients with psoriasis and the possible strategies to optimize it are shown in Table 1.

USEFUL THERAPIES IN CARDIOVASCULAR PREVENTION

Statins

Statin utilization is the cornerstone of cardiovascular risk management. The robust evidence showing a reduction of cardiovascular events has made statins essential in a variety of clinical conditions with elevated cardiovascular risk. To date, until now, no randomized studies were conducted to assess the impact of statins specifically in a population with psoriasis. Consequently, the available evidence in the population with psoriasis is weaker, although it suggests that this drug improved lipid levels and cardiovascular outcomes similarly in the subjects with or without psoriasis. In that sense, a post hoc analysis assessed patients from one primary cardiovascular prevention statin trial (Collaborative AtoRvastatin Diabetes Study (CARDS)] and two secondary cardiovascular prevention statin trials [Treating to New Targets (TNT) and Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL)] [77]. In this report, similar apolipoprotein B, total cholesterol and LDL cholesterol reductions occurred with statin therapy in patients with or without psoriasis. Additionally, high-dose atorvastatin significantly reduced cardiovascular events vs. standard/low-dose statins in patients with psoriasis in TNT/IDEAL trials.

To determine whether a patient is a candidate for statin therapy, clinicians must first determine the patient's risk of having a future cardiovascular event. However, clinicians' ability to—accurately—identify patient's true risk is imperfect, because the current available risk estimation tools have been shown to underestimate the risk in patients with chronic inflammatory diseases [60, 78, 79].

A recent study evaluated two cardiovascular prevention strategies in patients with psoriasis, analyzing which proportion of patients would be candidates to receive statin therapy [80]. The first, recommended by the European Society of

Cardiology (ESC), the European Society of Atherosclerosis (EAS) and the European League Against Rheumatism (EULAR), is to adjust the risk calculated by a multiplying factor (1.5 ×) and follow the recommendations for statin therapy of the general population [64, 65]. The second strategy considers psoriasis as a clinical situation that increases cardiovascular risk and consequently favors the indication of statins at least in subjects with intermediate risk. In this case, no adjustment factor is suggested. This strategy is recommended by the new American College of Cardiology/American Heart Association (ACC/AHA) guidelines for cholesterol management introduced at the end of 2018 [81]. According to the results of this study, the authors believe that not all patients with psoriasis should receive statins. Using both strategies, the proportion of eligible patients for statin therapy was similar (close to 60%). European and North American strategies agree that patients in primary prevention with diabetes and/or a level of LDL cholesterol > 190 mg/dl should receive statins whether they have psoriasis or not. The other group of patients who are candidates for statins should be defined according to the estimated cardiovascular risk. However, the concordance between both strategies in selecting patients with statin indication was moderate, indicating that individually some subjects had different indications according to the guideline used.

Patients with a previous vascular history (secondary prevention) should receive statins independently whether they have psoriasis or not, preferably of high intensity. Statins are considered "high intensity" when they can decrease LDL cholesterol > 50%.

Nonetheless, statins have pleiotropic effects including decreasing inflammation and may have the potential to reduce psoriasis severity. However, the results of studies on the effect of statins on the clinical course of psoriasis are not consistent. Although many investigators have reported that statins reduce the risk of psoriasis progression [82–84], some evidence suggests that statins may worsen psoriatic skin lesions [85, 86]. A meta-analysis of randomized clinical trials showed that statin therapy may improve psoriasis, particularly in patients with severe disease. The improvement in psoriasis severity (PASI) was significantly greater in patients who received statins than in those who received comparators [87].

The suggested recommendations for statin indication are shown in Table 2.

Aspirin

Nonsteroidal anti-inflammatory drugs have been associated with exacerbations of psoriasis. However, a recent review did not find an association between the use of aspirin and the risk of developing psoriasis or psoriatic arthritis [88].

Treatment with aspirin (in antiplatelet doses) and methotrexate seems to be safe, but it is advisable to control liver function [89]. We found no evidence that specifically analyzed the role of aspirin in cardiovascular prevention in patients with psoriasis.

Antihypertensive Therapy

Some antihypertensive drugs, especially beta blockers, have been linked to exacerbations of psoriasis [90–92]. However, most of the data come from case-control studies or case series, which limits the possibility of adjudicating causation. A large cohort showed that in hypertensive patients only the use of beta blockers for > 6 years, and not other antihypertensives, was associated with an increased risk of developing psoriasis [93]. A recent review showed that in patients taking beta blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptors blockers, psoriasis can be exacerbated [94].

Beta blockers can block beta-adrenergic receptors in the skin. This leads to a decrease in cell levels of cyclic adenosine monophosphate, an intracellular messenger involved in differentiation and inhibition of cell proliferation. In addition, beta-blockers have been reported to increase phosphorylation in T cells and favor excessive enzymatic release from lymphocytes, neutrophils and macrophages, favoring cellular hyperproliferation and psoriasiform change [95, 96]. Finally, in hypertensive patients, psoriasis was associated with a higher probability of

Table 2 Main indications for the use of statins in patients with psoriasis

Patient group	Statin intensity[a]
Secondary prevention (history of coronary heart disease, vascular brain disease or peripheral arterial disease)	Start high-intensity statin therapy
Primary prevention	
(a) Diabetes mellitus	Start moderate/high-intensity statin therapy[b]
(b) Severe hypercholesterolemia (LDL-C > 190 mg/dl or familial hypercholesterolemia)	Start high-intensity statin therapy
(c) Moderate to severe chronic renal insufficiency without hemodialysis (eGFR between 30 and 59 ml/min/1.73 m^2 or < 30 ml/min/1.73 m^2, respectively)	Start moderate statin therapy
(d) High cardiovascular risk score (after adjusting for the multiplier factor)	Start high-intensity statin therapy
(e) Moderate risk score (after adjusting for the multiplier factor) with some associated cardiovascular risk factor	Start moderate intensity statin therapy
(f) Subclinical atheromatosis	Start moderate/high-intensity statin therapy

[a] High-intensity statins: when reducing the LDL-C level ≥ 50% (atorvastatin 40–80 mg/day, rosuvastatin 20–40 mg/day). Moderate intensity statins: when reducing the LDL-C level 30–50% (atorvastatin 10–20 mg/day, rosuvastatin 5–10 mg/day, simvastatin 20–40 mg/day, fluvastatin 80 mg/day, pitavastatin 2–4 mg/day)

[b] In patients with more risk, with associated cardiovascular risk factors or white organ damage, it is reasonable to administer high doses of statins

having poorly controlled blood pressure, mainly in those with more severe psoriasis [97].

Hypoglycemic Agents

There is increasing evidence to suggest that several hypoglycemic agents used in the treatment of type 2 diabetes, including glucagon-like peptide-1 receptor (GLP-1) agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones and biguanides, exert beneficial effects on psoriasis. Within the mechanisms proposed to explain these findings are weight loss, glycemic control and the direct effect on inflammation pathways [98].

Regarding biguanides, the most frequently used antidiabetic drugs, the evidence suggests that metformin therapy can lower the risk of psoriasis development in patients with diabetes [99, 100]. Likewise, an open-label randomized controlled trial demonstrated improvement of psoriasis with metformin treatment compared with placebo [101].

Several reports demonstrated improvements in psoriasis with GLP-1 agonists [102–105]. Nevertheless, a randomized controlled trial conducted in patients with psoriasis and obesity showed no statistically significant difference in either the PASI or Dermatology Life Quality Index with liraglutide treatment compared with placebo [106].

Similarly, various reports have described improvement in psoriasis after treatment with DPP-4 inhibitors [107–109]. Additionally, a large-scale population-based retrospective study found that DPP-4 inhibitor therapy led to a reduced incidence of autoimmune disorders including psoriasis [110].

As with other drug groups, there is evidence that associates thiazolidinediones (especially with pioglitazone) with a lower incidence of psoriasis and, in those subjects with established

diagnosis, an improvement in the disease [111, 112].

Previously, the sodium glucose cotransporter-2 (SGLT-2) inhibitors have been reported to be associated with serious skin and subcutaneous tissue disorders [113]. However, recent research suggests that such findings would be specific for ipragliflozin and not with other drugs of the same group. We do not have evidence on the effect of these new drugs on psoriasis.

IMPACT OF SPECIFIC TREATMENTS FOR PSORIASIS ON CARDIOVASCULAR RISK

The choice of topical or systemic treatment depends on the severity, extent, risk-benefit ratio, patient preferences and the response to the therapy employed. Being a recurring pathology, it is common that multiple periods of treatments are required to maintain control of the disease. Systemic conventional treatments should be used with caution in psoriatic patients with MetS, because they could adversely affect the coexisting metabolic disorders, especially in the case of their chronic use [114]. Biologics appear to have a different safety profile compared with conventional treatments, and so they are usually tolerated.

A meta-analysis of observational studies that mostly analyzed works on rheumatoid arthritis but that included six studies conducted in patients with psoriasis demonstrated a cardioprotective effect of methotrexate, reducing cardiovascular events and acute myocardial infarction [115].

Retinoids can increase the value of triglycerides and cholesterol, and decrease the values of HDL cholesterol [116]. The effect is dose dependent and can be managed in most cases with diet or dose adjustment.

Some reports showed an increase in the level of triglycerides and total cholesterol, and a systematic review found a significant (dose-dependent) increase in blood pressure with the use of cyclosporine in patients with psoriasis [117].

The aforementioned meta-analysis also demonstrated a cardioprotective effect of anti-TNF, reducing cardiovascular events and acute myocardial infarction [115]. Specifically, in patients with psoriasis, Wu et al. showed that the incidence of acute myocardial infarction was significantly lower in the group treated with anti-TNF compared with those who received topical treatments (3.05 vs. 6.73 events every 1000 patients/year), without finding differences from the group treated by other systemic treatments [118]. Likewise, another recent meta-analysis considering only studies that included patients with psoriasis or psoriatic arthritis showed that the use of anti-TNF was associated with a lower risk of acute myocardial infarction and cardiovascular events regarding topical treatment or phototherapy [119]. However, infliximab therapy was associated with an increase in hospitalizations and higher mortality in patients with heart failure, although etanercept did not show such effects [120]. In another analysis of psoriasis patients treated with etanercept, the appearance of heart failure was rare and a real increase in risk could not be demonstrated [121]. In a meta-analysis conducted by Singh et al., the rate of heart failure was not statistically different when comparing therapy with biologics and controls [122].

IL-17A inhibitors (secukinumab and ixekizumab) do not appear to be associated with an increased risk of cardiovascular events, although the data are still limited [123]. Some small randomized trials showed a greater number of cardiovascular events with one of the IL-12/23 inhibitors, briakinumab, already discontinued in the market [124, 125]. However, a systematic review did not find this association with another drug in the same group (ustekinumab) [123].

Finally, while treatment with tofacitinib is associated with a small increase in cholesterol levels, the total/HDL cholesterol ratio does not change, there are no unfavorable changes in several cardiovascular risk factors, and the incidence of major cardiovascular events is low [126].

CONCLUSION

Psoriasis is a chronic inflammatory skin disease associated with increased cardiovascular

morbidity and mortality. Patients with psoriasis have an increased prevalence of classic cardiovascular risk factors, but psoriasis may provide an additional and independent cardiovascular risk factor: inflammation. Knowledge of the application of different strategies in cardiovascular prevention could mean an advantage in performing the difficult task of estimating cardiovascular risk and treating cardiovascular risk factors in this particular group of patients.

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