Potential Cardio-protective Effects of Psoriasis Medications

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Received: November 28, 2017
Accepted: July 11, 2018

ABSTRACT Psoriasis management can be challenging, complicated sometimes by being associated with other systematic inflammatory diseases including metabolic syndrome, myocardial infarction, hypertension, obesity, diabetes mellitus, and hyperlipidemia. Of particularly concern is its cardiovascular linkage. It is noteworthy and reassuring that some therapeutic options for psoriasis may be cardio-protective. We highlight phototherapy, methotrexate, and TNF alpha inhibitors and other biological agents for psoriasis that may lower the risk of cardiovascular events. Ways to reduce cardiovascular risk in patients with psoriasis should be encouraged. We concur with the conclusion that long-term study is necessary to assess the risks and benefits of biologic therapy, but that persons with preexistent cardiovascular disease or at high risk for it might benefit from medication with cardio-preventive value.

KEY WORDS: cardio-protective effects, psoriasis medications

INTRODUCTION

Psoriasis is a systematic chronic inflammatory autoimmune disease (1). It had been deemed as a keratinocyte dysfunction disorder, later as an immunologic disease, more recently as an interleukin (IL)-12/Th1-mediated process, and now as an IL-23/Th17-mediated condition, with multiple therapeutic approaches targeting IL-12/IL-23, IL-23, IL-17, and IL-17R. As an interleukin (IL)-12/Th1-mediated disease, therapy options include anti-CD2, anti-CD11a, and tumor necrosis factor-alpha blockers.

Common psoriasis can be viewed as more than a skin disorder (2). The disease process has been associated with many other systematic inflammatory diseases, including but not limited to arthritis, metabolic syndrome, myocardial infarction, hypertension, diabetes mellitus, and hyperlipidemia (2-4). For every 10% increase in body surface area for patients with psoriasis, there was an approximately 20% higher hazard of diabetes (5). This association is not only limited to adults, but to the pediatric population as well. In a study from the Nationwide Inpatient Sample, pediatric psoriasis was significantly associated with obesity, hypertension, diabetes, and arrhythmia (6). The cardiovascular system linked with psoriasis is of particular importance due to increased morbidity and mortality (7). There have been studies showcasing the effects of TNF alpha inhibitors, methotrexate, and other biological agents reducing the risk of cardiovascular events in patients with psoriasis (8-11). The inhibition of the inflammatory process from these drugs protects the heart from damage, reducing inflammatory changes of the epithelial tissue (2,12). We review the cardio-protective properties of commonly used drugs for treatment of psoriasis. Although recommending psoriasis therapy solely based on cardiovascular impact is probably unwise, for systemic

therapy with cardiovascular disease or a high risk of it, TNF alpha inhibitors and methotrexate offer the best evidence of benefit (2,8,10,11).

Pathogenesis of cardiovascular effects due to psoriasis

The process of the systematic inflammation from psoriasis is complex. Psoriasis has been associated with numerous cardiovascular problems including coronary atheromas, atherogenesis, increased coagulation, atheromatous plaques, and systolic/diastolic dysfunction as shown in Table 1. T-helper cells include Th1, Th2, and Th17 cells, the latter secreting the pro-inflammatory cytokine interleukin-17A, which helps recruit neutrophils. IL-23 induces the differentiation of naive CD4+ T-cells into Th17 cells that produce IL-17, IL-17F, IL-6, and TNF-α (13,14). Furue *et al.* (13) suggested that the initial trigger of psoriasis is due to the activation of plasmacytoid dendritic cells, which are stimulated from damaged keratinocytes by the host DNA and antimicrobial peptide LL-37 (15-17). The activated plasmacytoid dendritic cells produce TNF-alpha, IL-12, and IL-23, whereas IL-23 activates IL-17 producing effector cells. These cells produce IL-17A which bind to receptor IL-17, which downregulates the differentiation of keratinocytes and upregulates its proliferation, including recruiting neutrophils in the inflammatory process (13). A pivotal factor is the accumulation of proinflammatory cytokines such as TNF-alpha, which induces systematic inflammation and ultimately systematic diseases including cardiovascular diseases, type 2 diabetes mellitus, and obesity (13). Mehta *et al.* found that 76.9% of the 438 genes increased in psoriasis were also elevated in advanced stage atherosclerotic plaques, and the gene set was disproportionately induced by IFN-gamma and TNF-alpha (14). In the same study, INF-gamma and TNF-alpha receptors were increased in coronary atheromas compared with healthy coronary vascular tissue, and circulating TNF-alpha and INF-gamma were higher in the serum of patients with psoriasis. INF-gamma and TNF-alpha are thought to induce a pro-inflammatory response in endothelial and atherosclerotic tissues and could be a possible mechanism due to which patients with psoriasis have a higher incidence of cardiovascular disease (18-25).

In addition, homocysteine and endocan may play a role in cardiovascular diseases and act as biomarkers (26). High levels of homocysteine increase oxidative stress, cause endothelial dysfunction and atherogenesis, and activate the coagulation cascade (27,28). Increasing levels of serum homocysteine correlate with disease severity but not with duration of psoriasis (29,30). However, Ozden *et al.* (26) showed no correlation with disease severity or duration. Therefore, the homocysteine serum concentration could be an independent risk factor for the assessment of cardiovascular risk. Endocan stimulates the proliferation and migration of vascular smooth muscle cells, which increases the development of atheromatous plaques (26,31). Endocan may act as a potential biomarker for disease severity and duration based on the concentration (26,32). Ozden *et al.* and Orem *et al.* showed a significant association between left ventricular asynchrony in patients with psoriasis compared with controls, and the Tei index, which measures both global systolic and diastolic function, was also significantly higher for patients with psoriasis, possibly due to increased inflammation through cytokine stimulating keratinocyte proliferation and/or secondary amyloid deposition (26,33). Both these parameters could be used for future findings in patients with psoriasis to determine cardiac involvement.

Methotrexate and psoriasis-related cardiovascular effects

Methotrexate is a folate analogue commonly used for the treatment of psoriasis. Its effects lower inflammation and hyperhomocysteinemia, which are both potential causes of the cardiovascular diseases associated with psoriasis (1,18). Methotrexate has been found to reduce the incidence of cardiovascular-related diseases in patients with psoriasis. In a study performed with 7,615 American military veterans with psoriasis, those prescribed methotrexate were

Table 1. Cardiovascular problems associated with psoriasis

CARDIOVASCULAR PROBLEM	MECHANISM
Coronary atheroma	Increased levels of TNF-alpha and INF-gamma
Atherogenesis	Increased levels of homocysteine
Increased coagulation	Increased levels of homocysteine
Atheromatous plaques	Increased levels of endocan
Systolic/Diastolic dysfunction	Increased cytokines and/or amyloid deposition

Acta Dermatovenerol Croat
2018;26(3):249-254

found to have a relative risk of 0.73 compared with those who were not taking methotrexate, with a 95% CI of 0.55-0.98 (18). In a review of international cohorts, methotrexate significantly reduced the rate of myocardial infarction in patients compared with topical treatment (OR of 0.45 with a 95% CI of 0.28-0.73) (2). In a systematic review and meta-analysis study of rheumatoid arthritis and psoriasis, the pooled odds ratio was 0.73 with a 95% CI of 0.70-0.77, showing a significant decrease in the risk of cardiovascular events with methotrexate (19). Another meta-analysis showed methotrexate was associated with a 21% lower risk of total cardiovascular disease (95% CI of 0.73-0.87), although out of the 10 studies only one looked at psoriasis and the other nine studied rheumatoid arthritis (20). Regardless of the limited number of studies performed with psoriasis compared with rheumatoid arthritis, methotrexate has been shown to have cardiovascular protective effects in patients with psoriasis.

TNF-alpha inhibitors and psoriasis-related cardiovascular effects

It has been postulated that IFN-γ and TNF-α work synergistically in both psoriasis and atherogenesis, possibly linking these two processes in some patients (34-42). TNF-alpha inhibitors and methotrexate have been used for the treatment of psoriasis. TNF-alpha is a pro-inflammatory cytokine which stimulates keratinocyte production and activates dermal macrophages and dendritic cells which are thought to be imperative to the pathogenesis of psoriasis and cardiovascular events (13,21). A 2-year study of carotid intima-media thickness showed a significant reduction from 0.70 to 0.63 with patients on long-term TNF-alpha inhibitors, compared with a significant progression from 0.79 to 0.82 with patients who were naïve to TNF-alpha inhibitors (22). In a retrospective cohort study of patients with psoriasis, the incident rates of MI for TNF-alpha inhibitors, oral/phototherapy, and topical cohorts were 3.05, 3.85, and 6.73 per 1000 patient-years, respectively (43). The TNF-alpha inhibitor cohort had a statistically significant 55% reduction (0.45 RR with 95% CI of 0.30-0.68) in MI incidence compared with the topical cohort. In a study comparing TNF-alpha inhibitors and methotrexate, the major cardiovascular events hazard was 45% (0.55 HR with a 95% CI of 0.45-0.67), lower for the TNF-alpha cohort than for the methotrexate cohort (7). TNF-alpha inhibitors have also been shown to decrease atherosclerosis progression in men; this association remained statistically significant (adjusted β coefficient=-2.09, 95% CI -3.32, to 0.86; $P<0.001$) even after

Table 2. Medications and psoriasis

MEDICATION	MECHANISM	RESULTS FROM STUDIES
Methotrexate	Folate analogue lowering inflammation and hyperhomocysteinemia	RR 0.73 in reduced incidences of cardio-related diseases compared with not taking methotrexate (18) OR 0.45 in reduced rate of MI compared with topical treatment (2) OR 0.73 in patients with RA and psoriasis for cardiovascular events (19)
TNF-alpha inhibitors	Inhibits TNF-alpha which decreases levels of inflammation	Significant reduction of carotid intima-media thickness from 0.70 to 0.63 (22) RR 0.45 in MI incidence compared with topical cohort (43) 0.55 HR for major cardiovascular events compared with methotrexate cohort (7) Adjusted β coefficient -2.09 for decreased atherosclerosis progression in men (42)
IL-23 and IL-17 inhibitors	Antibodies against immunoglobulins associated with inflammation	No known studies featuring cardio-protective effects
Phototherapy	Alteration of cytokine profile, induction of cellular apoptosis, immunosuppression promotion and downregulation of IL-17	Significant resistin levels from 9.02+/-8.83 ng/mL to 4.86+/-3.30 ng/mL (39) TNF-alpha levels were significantly reduced from 1.60 to 1.30 for PUVA and 1.10 to 0.80 for NBUVB and CRP levels were significantly reduced from 3.90 to 2.59 for PUVA and 2.35 to 2.32 for NBUVB (35)

RR: Relative risk; OR: Odds ratio; HR: Hazards ratio; MI: Myocardial infarction; RA: Rheumatoid arthritis

controlling for cardiovascular risk factors and lipid-lowering drugs (41). Among men, TNF-alpha inhibitors were also associated with a reduced rate of atherosclerosis progression compared with non-biologic anti-psoriasis medications and compared with no systemic anti-psoriatic therapy (41). However, TNF-alpha inhibitors are well-known risk factors for heart failure, especially infliximab, which has been shown to increase hospitalizations, morbidity, and mortality (42).

IL-23 and IL-17 inhibitors and psoriasis

The IL-23/Th17-mediated disorder known as psoriasis has been treated with several novel drugs targeting IL-12/IL-23, IL-23, IL-17, and IL-17R. Inhibiting IL-23 and IL-17 is one approach (13,23). The first medication approved by the Food and Drug Administration (FDA) and most commonly employed is ustekinumab, a monoclonal antibody directed against IL-23 and IL-12 (23). Three IL-17 antagonist drugs (secukinumab, ixekizumab, and brodalumab) were recently approved for treatment of psoriatic diseases (24). Common side-effects associated with these medications include upper respiratory infections, headache, pain, and nasopharyngitis (23,24). Myocardial and cerebral infarctions were observed in patients during the clinical trials of ustekinumab, although they were limited to 2 events and 1 event, respectively (23). In a clinical trial follow-up with ustekinumab, cumulative rates of 0.56 and 0.46 adverse cardiovascular events per 100-patient years were reported in patients treated with 45 mg and 90 mg, respectively. These results were consistent with those in the general and psoriasis populations (25). However, to our knowledge there have not been any studies on cardio-protection regarding these biological agents, unlike methotrexate and TNF-alpha inhibitors.

Phototherapy and psoriasis

As psoriasis is an inflammation-mediated disease, it is associated with a number of markers of inflammation, including C-reactive protein, IL-6, and homocysteine (34). In addition, psoriasis has been associated with insulin resistance, and elevation of leptin and resistin, which act as biomarkers, has been reported (2,35). Phototherapy is a good treatment option for psoriasis. Its mechanism of action for treatment has been associated with its alteration of the cytokine profile, induction of cellular apoptosis, and immunosuppression promotion as well as the downregulation of the IL-17 pathway (36,37). In a study with 50 subjects with psoriasis, a significant decrease in the number of subjects who met the IDF metabolic syndrome criteria was documented after treatment with narrow-band UVB (NB-UVB) (38). Another study demonstrated a significant decrease ($P<0.001$) in resistin levels after bath PUVA or NB-UVB from 9.02+/-8.83 ng/mL to 4.86+/-3.30 ng/mL (39). In addition, it documented a correlation between decreased resistin levels and the Psoriatic Area Severity Index (PASI) score, suggesting that the phototherapy and resistin levels are clinically relevant (39). In a prospective study comparing topical therapy with calcipotriol and betamethasone dipropionate versus NB-UVB and PUVA, NB-UVB showed a significant reduction in TNF-alpha and CRP, while PUVA also showed a significant reduction not only in the same biomarkers, but also in IL-6 and a significant increase in adiponectin, a protein involved in fatty acid breakdown (35). Phototherapy increases vitamin D, which can lead to better insulin secretion and sensitivity (34). However, the relevance of vitamin D in psoriasis is debatable; further evidence should be pursued regarding the value of vitamin D supplementation (40) (Table 2).

CONCLUSION

Based on a number of studies involving methotrexate and TNF-alpha inhibitors, these medications appear to provide cardio-protective effects for patients with psoriasis. Therefore, they should be considered with patients who have cardiovascular comorbidities along with psoriasis. Evaluation of antibody inhibitors of IL-23 and IL-17 should be compared with methotrexate and TNF-alpha inhibitors in terms of heart-related effects. More studies should be pursued regarding these novel biological agents and their effects on the cardiovascular system.

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