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PSORIASIS (JAISHIN WU, SECTION EDITOR)

Effects of Biologic Therapy on Cardiovascular Disease in Psoriasis

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Abstract

Purpose of Review The aim of this review is to summarize the literature on the effects of biologic treatment for psoriasis on the risk of cardiovascular (CV) disease (CVD) and adverse CV outcomes.

Recent Findings Therapy with tumor necrosis factor-alpha (TNF-α) inhibitors has been associated with reduced risk of CV events in observational studies; however, data are conflicting. Data on interleukin (IL)-17 and IL-12/23 inhibitors are limited, and primary endpoints of studies on these drugs have not been focused on CV outcomes.

Summary Psoriasis is a chronic inflammatory skin disease that has distinct pathogenetic overlaps with that of atherosclerosis. Patients with psoriasis, in particular moderate-to-severe disease, have an increased incidence and prevalence of CV risk factors and CVD. Biologic therapies targeted for treatment of psoriasis dampen the systemic inflammation and may therefore be effective in treating not only the cutaneous manifestations of psoriasis, but may also have beneficial or detrimental CV effects depending on the particular cytokine target and mode of action. Studies on TNF-α inhibitors have suggested that these may reduce the coronary artery calcium score, improve myocardial function, and reduce the risk of adverse CV events albeit that use of these drugs may also lead to weight gain. Studies of treatment with anti-IL-12/23 agents have yielded conflicting results, but ustekinumab, the only IL-12/23 inhibitor currently approved for psoriasis, appears to be effect neutral on CV parameters. Newer drugs such as IL-17 inhibitors have not demonstrated any notable CV safety signals based on pivotal clinical trials, but long-term data from real-life studies are lacking. As new treatment modalities emerge, there is a need for well-powered long-term observational studies to firmly establish the CV safety profile of these drugs in a real-life setting.

Keywords Psoriasis · Cardiovascular disease · Biologics therapy · Drug safety · Inflammation

Introduction

Psoriasis is a chronic immune-mediated inflammatory skin disorder with widespread implications [1]. The disease is mediated by a systemic inflammatory response with an increased presence of T-helper cells (Th), such as Th-17 and pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-17, and IL-23 [2, 3]. Numerous studies have associated psoriasis with cardiovascular (CV) risk factors [4–9] and CV disease (CVD) [10, 11]. Although psoriasis may be brought to long-term remission, it cannot be cured, and treatment may often be lifelong [12]. The understanding of the role of immuno-inflammation in the pathogenesis of psoriasis has facilitated the development of biologic therapies targeted against specific cytokines [1]. Similar to psoriasis, atherosclerosis is mediated by a pro-inflammatory response [13, 14]. It has therefore been suggested that systemic anti-inflammatory treatment of psoriasis could not only improve the cutaneous manifestations [1] but also reduce the risk of CVD [15–17]. The aim of this review is to summarize the literature on biologic treatments for psoriasis and their effects on the risk of CVD and adverse CV outcomes.

This article is part of the Topical Collection on *Psoriasis*

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Inflammation

A dysregulated immune system is essential in the pathogenesis of psoriasis [3]. Keratinocytes produce the antimicrobial peptide LL-37 that activate plasmacytoid dendritic cells (DC) and myeloid DC [2]. Myeloid DC release IL-23 that stimulates Th-17 cells to produce cytokines including IL-17, resulting in keratinocyte proliferation and promotion of the

inflammation [2, 3]. Psoriasis and atherosclerosis share important immunological characteristics including inflammatory cytokines IFN-γ and TNF-α [18]. Also, IL-17, intracellular adhesion molecules (ICAM), vascular cell adhesion molecules (VCAM-1) [18], and selectins [19] are present in both conditions.

Psoriasis and Cardiovascular Disease

Severe psoriasis is associated with hyperlipidemia [6] and lowered high-density lipoprotein (HDL) efflux capacity, factors implicated in coronary artery disease [20]. Moreover, psoriasis is associated with hypertension independently of conventional CV risk factors [8]. Furthermore, obesity occurs more frequently among psoriasis patients [6, 7], even in young individuals [4], in a psoriasis severity-dependent manner [6]. Furthermore, psoriasis patients have increased risk of diabetes [5, 6, 9], and patients with severe psoriasis are more likely to develop it than patients with mild psoriasis [6]. Overall, psoriasis is associated with CV risk factors and patients with severe psoriasis have an increased risk of myocardial infarction (MI) [10, 11], stroke, and CV death [11]. Interestingly, in patients with psoriasis, the relative risk of adverse CV outcomes appears to be highest among younger individuals [10].

TNF-α Inhibitors and Cardiovascular Risk Factors

TNF-α is a pro-inflammatory cytokine, which is produced in various tissues by a number of cells, including macrophages, T cells, and keratinocytes [21]. Treatment with TNF-α inhibitors prevents TNF-α from binding to its receptors and hinders the inflammatory process [22]. In patients with psoriasis, treatment with TNF-α inhibitors did not significantly change cholesterol levels after 3 months of therapy in a prospective observational study [23], or after 6 months of therapy in a retrospective cohort study with 141 psoriasis patients [24], respectively. The latter study also reported that treatment with infliximab and etanercept was significantly associated with weight increase compared to methotrexate (MTX) treatment after 6 months [24]. Similarly, stable lipid levels were found in a prospective, controlled, interventional, observer-blinded study, where psoriasis patients were treated with adalimumab, etanercept, or infliximab for 13 months [25••]. A study from 2013 with psoriasis patients randomized to adalimumab or non-systemic treatment (topical therapies or phototherapy) showed no change in total cholesterol, HDL, low-density lipoprotein (LDL), or triglycerides after 15 weeks of treatment [26].

Looking at hypertension, a murine model of psoriasis showed increased systolic blood pressure and endothelial dysfunction compared to non-psoriatic mice [27]. After 10 weeks of etanercept treatment, the vascular function was somewhat restored [27]. A recent prospective, controlled, interventional, observer-blinded clinical study of 58 patients with psoriasis examined the effects of adalimumab, etanercept, and infliximab on the development of atherosclerosis during a 13-month period using computed tomography (CT) imaging [25••]. Exclusion criteria included symptoms of coronary artery disease, major uncontrolled CV risk factors, prior CV events, or coronary artery revascularization [25••]. At follow-up, the patients who had not received TNF-α inhibitors demonstrated a significant progression of the calcium artery score, whereas the TNF-α inhibitor-treated interventional group did not [25••]. After excluding four patients who had received non-TNF-α inhibitor treatment, the results remained significant [25••]. Another experimental study assessed vascular inflammation in the carotid artery and in the ascending aorta using positron emission tomography-CT (PET/CT) in 30 psoriasis patients randomized to either adalimumab or non-systemic treatment (i.e., topical or phototherapy) [26]. Inclusion requirements were a history of coronary atherosclerosis or a minimum of three CV risk factors, and a first-degree relative with coronary atherosclerosis under the age of 65 [26]. After 15 weeks of treatment, there was a significant reduction in the inflammation as measured by the average of maximum target-to-background ratio in the carotid arteries and ascending aorta for patients treated with adalimumab, and a non-significant reduction for the non-systemic treatment group [26]. The change between the two treatment groups did not reach statistical significance [26]. This might be due to that this study examined the artery with the highest target-to-background ratio [26]. Along the same line, a recent randomized, double-blinded study measured vascular inflammation by PET/CT in 107 psoriasis patients. The results indicated no difference between patients receiving adalimumab or placebo after 16 weeks [28•]. These conflicting results may be attributed to study populations with distinct CVD history and risk factors, limited number of included patients, and different lengths of follow-up [25••, 26, 28•]. Additionally, in psoriasis patients, the ascending part of the aorta may not be inflamed, as is the rest of the aorta and furthermore less frequently have atherosclerotic plaques [29].

In a prospective observational study with echocardiographic data on 18 subjects treated with TNF-α inhibitors and IL-12/23 inhibitors, an improvement in myocardial function was found [23]. Similarly, right ventricular systolic function was improved in a 30-month study of 44 psoriasis patients treated with adalimumab, infliximab, or etanercept [30]. Lastly, some small but not all studies have found improvements in insulin sensitivity [31, 32], as well as a lowered risk of diabetes [33] during TNF-α inhibitor treatment of psoriasis. In summary, while treatment with some TNF-α inhibitors may confer a slight weight gain, these drugs appear to have a net benefit with regard to their effects on cardiometabolic parameters, albeit that the literature remains heterogeneous in part due to methodological differences.

TNF-α Inhibitors and Cardiovascular Events

In a retrospective cohort study from 2012, a total of 8845 patients with psoriasis were treated with either biologics (etanercept, infliximab, or adalimumab), systemic non-biologic agents (cyclosporine, acitretin, or MTX) or phototherapy (UVB or PUVA), or topical treatment alone [16]. In that study, treatment with TNF-α inhibitors was associated with reduced risk of first-time MI compared to topical agents, but no significant difference was seen when compared to systemic non-biologic agents or phototherapy. In a recent retrospective study, the risk of stroke, transient ischemic attack, and unstable angina was examined in 17,729 patients with psoriasis [17]. In multivariate analyses, patients treated with TNF-α inhibitors displayed a significantly lower risk for each endpoint when compared to MTX [17]. Furthermore, treatment with TNF-α inhibitors was associated with an 11% reduced risk for the aforementioned outcomes for every 6 months of additional treatment [17]. The differing results concerning treatment with MTX might be explained by the different study endpoints and patient exclusion criteria [16, 17]. Similarly, a study of 2400 patients with severe psoriasis reported lower event rates of CV death, MI, and stroke in patients treated with biologics, including TNF-α inhibitors, compared to other therapies (retinoids, cyclosporine, phototherapy, or climate therapy) [15].

In few retrospective cohort studies on patients with psoriasis, TNF-α inhibitors appear to lower the risk of MI compared to topical treatment.

IL-12/23 Inhibitors and Cardiovascular Risk Factors and Events

IL-23 stimulates T cells to produce inflammatory cytokines such as IL-17 that mediate the psoriasis-associated inflammation [2, 3]. Briakinumab and ustekinumab are monoclonal antibodies that bind a subunit of IL-12 and IL-23 and inhibit their cellular effect [34].

A meta-analysis from 2013 included nine randomized controlled, double-blinded studies of psoriasis patients treated with briakinumab or ustekinumab for 12 to 20 weeks [34]. Results showed that patients who received IL-12/23 inhibitors had higher odds of MI, cerebrovascular events, and CV death compared to placebo (OR = 4.23, 95% CI 1.07–16.75, p = 0.04) [34]. Another meta-analysis of 22 short-term randomized controlled trials studied the CV effects of briakinumab and ustekinumab in psoriasis patients [35] and found no increased risk of MI, cerebrovascular event, or CV death in patients treated with these drugs compared to placebo-treated patients. A number of explanations may exist for these conflicting results, including low statistical power [35], different statistical methods, and that the results were not adjusted for patient dropout [36]. A study of 5 randomized controlled phase II and III trials on moderate-to-severe psoriasis reported 27 major adverse cardiovascular events (MACE) (n = 19 MI, n = 3 stroke, n = 5 CV deaths) in patients treated with briakinumab [37]. When at least two out of four specific CV risk factors (including diabetes, history of CVD, body mass index [BMI] ≥ 30, and elevated baseline blood pressure) were present simultaneously, the relative risk of MACE was 7.58 compared to when one or zero risk factor was present [37]. Consequently, the development of briakinumab was discontinued after concerns of increased MACE risk [38]. Pooled data on 4 phase II and III trials with a total of 1582 psoriasis patients receiving ustekinumab yielded 5 MI, stroke, or deaths due to CVD, after 12 to 20 weeks of treatment, and zero among 732 patients receiving placebo [39].

A study of 2444 psoriasis patients showed no increased risk of MI, cardiac failure, CV death, acute coronary syndrome, hemiparesis ischemic stroke, or cerebrovascular accident from treatment with ustekinumab [40]. Similarly, in a study from 2013, 766 psoriasis patients were treated with ustekinumab [41]. After 5 years of treatment, no elevated risk of MI, stroke, or CV death was found. A more recent study evaluated treatment with ustekinumab, TNF-α inhibitors, and topical or phototherapy in 7550 psoriasis patients [42]. After a mean of 2.8 years, ustekinumab treatment was not associated with increased risk of stroke, MI, or CV death compared to topical treatment or phototherapy. The same was seen in a composite analysis of TNF-α inhibitors and ustekinumab [42].

Overall, while the development of briakinumab was discontinued due to CV safety concerns, the currently approved IL-12/23 inhibitor ustekinumab seems to be effect neutral on CV parameters in patients with moderate-to-severe psoriasis. Notwithstanding this, the current understanding of the role of IL-12 and IL-23 in atherosclerosis remains incomplete.

IL-17 Inhibitors and Cardiovascular Risk Factors and Events

IL-17 is a family of pro-inflammatory cytokines comprising several subtypes predominantly secreted by Th-17 cells [43]. IL-17A is believed to be the subtype particularly involved in inflammation [43] and when bound to a receptor in the cell membrane, it activates downstream mechanisms inducing inflammation [43]. Monoclonal antibodies, including secukinumab and ixekizumab, target IL-17A, whereas brodalumab binds to the IL-17 receptor [44]. In an animal model of a psoriasis-like skin disease, an overproduction of IL-17 led to increased arterial blood pressure and endothelial dysfunction [27]. Elevated intracellular total cholesterol levels accompany IL-17 signaling, which help elucidate the link between psoriasis and dyslipidemia [45]. A phase II trial randomized patients with psoriasis to either placebo or secukinumab and found no increase in lipid levels at the end

of the study [46]. Moreover, a safety analysis of clinical trials collected data mainly from three randomized, double-blinded, placebo-controlled trials; there was no change in glucose levels, blood pressure, body weight, or lipids for patients receiving ixekizumab compared to placebo [47].

Overall, data on IL-17 inhibitors are limited to few short-term studies predominantly from pivotal trials, and future long-term studies of this drug class are needed.

There are clinical trials exploring the efficacy and safety of IL-17 inhibitors in patients with psoriasis [46–49]. One phase III trial randomized psoriasis patients to secukinumab, etanercept, or placebo for a year. At the end of the study, comparable numbers of MACE were reported for secukinumab ($n = 2$) and etanercept ($n = 1$), whereas no events were seen in the placebo group [48]. Similarly, 404 patients were randomized to treatment with either secukinumab or placebo, and results showed a higher number of cardiac disorders in the secukinumab group ($n = 9$) than in placebo ($n = 0$) [46]. A pooled analysis of 10 phase II and III randomized, double-blind studies included 3993 patients with moderate-to-severe plaque psoriasis [49]. The results showed comparable numbers of stroke, MI, and CV death for secukinumab 150 mg ($n = 4$, incidence rate (IR) 0.35 per 100 subject years [SYs]), secukinumab 300 mg ($n = 5$, IR 0.42 per 100 SYs), and etanercept ($n = 1$, IR 0.34 per 100 SYs) over 52 weeks [49].

A review with data from mainly three phase III trials on ixekizumab showed similar rates of MACE between ixekizumab and etanercept and low rates of MACE with continued exposure for ixekizumab until week 60 [47]. Limitations to these clinical trials are highly selected patients, short study duration that limits conclusions regarding the long-term safety [46, 47, 49], few observations of rare adverse events [48, 49], and short duration of treatment with placebo [48, 49] or TNF-α inhibitors [47] in relative few number of patients compared to the number of patients receiving IL-17 inhibitors [49]. Furthermore, conclusions are limited to patients with moderate-to-severe plaque psoriasis [46, 48, 49]. In a very recent real-life observational study of 195 patients treated with secukinumab for up to 2 years, four cardiovascular events were reported during therapy [50].

Overall, data from short-term safety and efficacy trials exploring IL-17 inhibitor treatment in patients with moderate-to-severe psoriasis suggest no increased CV risk compared to placebo or TNF-α inhibitors. Real-life observational registry data are emerging, but long-term follow-up is needed to adequately determine the safety profile of IL-17 inhibitors.

Conclusion

Psoriasis is associated with CV risk factors, such as hyperlipidemia, obesity, hypertension, diabetes, and tobacco smoking, and also confers an independent disease severity-dependent risk of CVD and MACE. Data from experimental and observational studies suggest that TNF-α inhibitors may have beneficial effects on CV risk factors and may reduce the prevalence and risk of CVD and CV events among patients with psoriasis. Treatment with IL-12/23 inhibitors appears to be effect neutral with regard to CV parameters, suggesting no net benefit or risk associated with use of these drugs. While early data on IL-17 inhibitors also suggest that these are safe to use in patients with psoriasis, data are scarce and predominantly based on pivotal clinical trials. Therapeutic dampening of the systemic inflammation in psoriasis may in part reduce the risk of future CV events, yet long-term observational data are warranted, and traditional CV risk monitoring and treatment is encouraged in these patients.

Compliance with Ethical Standards

Conflict of Interest Dr. Egeberg reports grants and personal fees from Lilly, grants and personal fees from Pfizer, personal fees from Novartis, personal fees from Janssen, personal fees from Samsung Bioepis, and personal fees from Galderma, outside the submitted work.

Dr. Skov reports personal fees from Pfizer, AbbVie, Eli Lilly, Novartis, and LEO Pharma, and has been a consultant or served on Advisory Boards with Pfizer, AbbVie, Janssen Cilag, Novartis, Eli Lilly, LEO Pharma, and Sanofi. She has served as an investigator for Pfizer, AbbVie, Eli Lilly, Novartis, Amgen, Regeneron, and LEO Pharma and received research and educational grants from Pfizer, AbbVie, Novartis, Sanofi, Janssen Cilag, and Leo Pharma, outside the submitted work.

Dr. Henning has nothing to disclose.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Recently published papers of particular interest have been highlighted as:

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- •• Of major importance

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