FEATURE ARTICLE

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Research Evidence for Reducing Cardiovascular Risk With Biologic Therapies in Patients Who Have Psoriasis

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ABSTRACT: Psoriasis is a skin disease associated with systemic inflammation affecting many people in today's society. Prevalent studies support a relationship between systemic inflammation and increased cardiovascular disease in these patients. The purpose of this article is to provide the research evidence that assessed the relationship between systemic treatments such as biologic agents for psoriasis and their effects on cardiovascular risk factors. The review of literature illustrates that patients treated with biologic agents have significantly lower cardiovascular disease as evidenced by biomarkers. Levels of evidence for each research study were assigned using a rating system. Findings, implications, and the need for further research on this topic are discussed.

Key words: Biologics, Biomarkers, Cardiovascular Risk, Psoriasis

INTRODUCTION

Psoriasis is a common skin disease that affects approximately 3% of the population in the United States (Armstrong, 2013). This disease usually presents itself on the skin with scaly plaques; however, it is becoming more widely accepted as not only a skin disease but also a systemic chronic inflammatory disease (Boehncke, Fichtlscherer, et al., 2011). It has been shown that, because of this systemic inflammation, patients with psoriasis have an increased prevalence of cardiovascular risk factors including a greater incidence of coronary artery disease, myocardial infarction (MI), and cardiovascular death compared with the general population (Armstrong, 2013). These comorbid conditions are thought to be secondary to chronically elevated levels of cytokines resulting from systemic inflammation (Villasenor-Park, Wheeler, & Grandinetti, 2012). These cytokines may include tumor necrosis factor alpha (TNF-alpha), interleukin-1 beta (IL-1 beta), and IL-17.

With increased understanding of the systemic pathology of psoriasis, targeted treatment therapies have emerged in recent years. In attempts to target TNF-alpha, a number of biologics such as infliximab, etanercept, and adalimumab have been developed for the treatment of psoriasis and other chronic inflammatory disorders (Channual, Wu, & Dann, 2009). Ustekinumab has also been developed and targets IL-12 and IL-23, and there may be other inflammatory cytokines that play a role in psoriasis and systemic inflammation (Villasenor-Park et al., 2012). Other widely used systemic therapies include methotrexate and cyclosporine (Bissonnette et al., 2013). Other nonsystemic treatments for psoriasis include topical treatments, corticosteroids, vitamin D analogues, dithranol, and tar (Wakkee, Thio, Prens, Sijbrands, & Neumann, 2007). These are commonly reserved for milder forms of psoriasis when systemic therapy is not warranted.

Systemic treatments continue to be very effective in the treatment of psoriasis (Yost & Gudjonsson, 2009). Furthermore, these therapies are not only reducing the burden of the skin disease but, with their targeted antagonist actions on systemic inflammation, are suggesting a beneficial decrease in cardiovascular risk. With emerging data on biologic therapies and their beneficial outcomes on suppressing systemic inflammation, change in treatment of patients with psoriasis is evolving. As Armstrong (2013) states: "Whether systemic treatments for psoriasis modify the risk of major adverse cardiovascular events is a clinically

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significant question." As this statement suggests, it is important to examine the best available evidence to determine this relationship and its clinical significance.

METHODS OF REVIEW

A literature search was conducted using the computerized databases of PubMed, CINAHL, Cochrane Library, UpToDate, Google Scholar, and Web of Knowledge. To identify pertinent studies within the past 5 years, various keywords and searches were utilized. Keywords used in the search included psoriasis, biologic therapy, and cardiovascular risk. To include all pertinent studies, broader and narrower topics were explored in the search. Broader topic keywords utilized included inflammatory disease, systemic treatment, and comorbidities. Narrower topic keywords utilized included plaque psoriasis, psoriasis vulgaris, infliximab, etanercept, adalimumab, ustekinumab, anti-TNF, systemic inflammation, MI, C-reactive protein (CRP), and biomarkers. An additional strategy used in the search to include all keywords was MeSH terminology in the PubMed database. Manual searches were also completed from the reference lists of various articles obtained. Inclusion criteria for research studies included systemic treatment methods as the intervention in patients with psoriasis within the past 5 years and published in peer-reviewed journals. No previous systemic reviews of the research literature were located on this topic.

STRENGTH OF EVIDENCE

To rate the strength of the studies retrieved in this review, a rating system by Melynk and Fineout-Overholt (2005) was used. These levels of evidence are the following: level 1, a systemic review or meta-analysis of randomized controlled trials (RCTs) or clinical practice guidelines based on RCTs; level 2, a well-designed RCT; level 3, well-designed non-RCTs; level 4, well-designed case control or cohort studies; level 5, systemic reviews of descriptive or qualitative studies; level 6, a single descriptive or qualitative study; and level 7, the opinion of expert authority. The seven studies reviewed are presented in Table 1 and include the appropriate ranking of level of evidence.

FINDINGS OF THIS REVIEW

Of the seven studies reviewed, one was an RCT level 2 (Bissonnette et al., 2013). Five studies were observational/cohort level 4 (Abuabara et al., 2011; Ahlehoff et al., 2013; Boehncke, Salgo, et al., 2011; Jokai et al., 2013; Wu et al., 2013). One study was a retrospective analysis of data from a RCT level 6 (Strober et al., 2008). In the studies reviewed, strengths and limitations were found. Internal validity was strengthened in the one study that used random assignment to groups (Bissonnette et al., 2013). Internal validity was also strengthened in the studies with large sample sizes, which included four studies (Abuabara et al., 2011; Ahlehoff et al., 2013; Strober et al., 2008; Wu et al., 2013). The reliability of measurement tools was noted in all the studies. For example, in one study, carotid and brachial intima-media thickness was measured by high-resolution, B-mode ultrasonography (Jokai et al., 2013). Another study strengthened internal validity with their measurement tool by using only two well-trained investigators with each participant being monitored by the same investigator at all visits (Boehncke, Salgo, et al., 2011).

Although there were many strengths to the studies reviewed, limitations were also found. The use of nonrandomized assignment to groups in many of the studies decreased internal and external validity by increasing selection bias and decreasing the generalizability of the study. As in one of the observational studies (Abuabara et al., 2011), patients were not randomized to treatment groups. One should note that there could be bias of primary differences in the patients. Decreased generalizability was seen in the study by Ahlehoff et al. because the participants included a Danish population only, which is predominantly persons of Caucasian decent. An additional weakness was that three studies had sample sizes of less than 50 participants (Bissonnette et al., 2013; Boehncke, Salgo, et al., 2011; Jokai et al., 2013).

All seven studies reviewed used outcomes of different measurements of cardiovascular risk. However, different measurements used showed an overall decrease in cardiovascular risk in patients with psoriasis being treated with systemic therapies (Bissonnette et al., 2013; Boehncke, Salgo, et al., 2011; Jokai et al., 2013; Strober et al., 2008). Abuabara et al. (2011) did not show a significant difference in MI risk between systemic treatment and phototherapy treatment. However, the risk of MI was lower in patients less than 50 years old in the systemic treatment group; a similar finding of a significant decrease of MI risk was seen with etanercept in the study by Wu et al. (2013). Cardiovascular risk was measured by CRP levels in one study, and the decrease in cardiovascular risk was seen with a decrease in CRP levels in participants treated with etanercept (Strober et al., 2008) similar to the decrease in highly sensitive-CRP (hs-CRP) levels with the adalimumab treatment group compared with a control group in a study by Bissonnette et al. In the study by Ahlehoff et al. (2013), a reduced risk of death and cardiovascular disease in participants on biologic or methotrexate treatment was found compared with other therapies. Three studies measured cardiovascular risk by other methods such as vascular inflammation (Bissonnette et al., 2013), vascular endothelial growth factor (Boehncke, Salgo, et al., 2011), and intima-medial thickness (Jokai et al., 2013). Vascular inflammation as measured by target background ratio was improved in adalimumab participants as compared with the control group (Bissonnette et al., 2013).

Nonsignificant results were also noted in the studies reviewed. No significant difference overall was seen in MI risk between systemic and phototherapy treatment groups in one study (Abuabara et al., 2011). Bissonnette et al. (2013) showed no statistically significant change

TABLE 1. Summary of Primary Research Studies Reviewed on Biologic Therapy for Psoriasis Treatment

Author (Year), Country	Design Sample, Size	LOE	Intervention/IV	Outcomes measures/DV and Measures of outcome	Results	Limitations
Abuabara, Lee, and Kimball (2011), United States	Observational cohort study: using medical and pharmacy administrative claims data from the United Health Group, May 2000–September 2008. *n* = 25,554: (a) systemic treatment (*n* = 20,094), (b) phototherapy (*n* = 4,220), and (c)both treatments (1,240 excluded from primary analysis)	4	Systemic therapy group (methotrexate, ciclosporin, alefacept, efalizumab, adalimumab, etanercept, and infliximab) compared with control group (UVB phototherapy)	MI incidence rates using the person–time method. ICD code for diagnosis of MI. Treatment data from pharmacy administration claim data from United Health group from May 2000 to September 30, 2008.	Hazard's ratio analysis found no significant difference in the risk of MI between patients receiving systemic therapy compared with patients receiving phototherapy. However, risk of MI was lower for patients <50 years old in the systemic group.	Participants not randomized to treatment group. The study tried to keep the control group and treatment group with similar disease severity; this could have excluded patients with severe disease on systemic treatment. Possible misclassification bias of diagnoses and outcomes.
Ahlehoff et al. (2013), Denmark	Retrospective longitudinal cohort study using Danish nationwide prospectively recorded registries. *n* = 2400: biologic = 693, methotrexate = 799, and other therapies = 908.	4	Three treatment groups: (a) biological agents, (b) methotrexate, and (c) other therapies	Incidence rates and hazard ratios of (a) death, MI, and stroke and (b) cardiovascular death, MI, and stroke.	Hazard's ratios were conducted. Systemic treatment with either biologic therapy or methotrexate was associated with reduced risk of death and lower cardiovascular disease event rates compared with the group receiving other therapies.	Danish-only population. Registry used does not hold information for other confounders in cardiovascular risk. Did not look at individual biologics and had a short follow-up period.
Bissonnette et al. (2013), Canada	Randomized control trial, *n* = 30	2	Randomized to control nonsystemic treatment group (topical therapies or phototherapy) or to receive adalimumab SQ for 4 months	Vascular inflammation was measured in the carotid artery and ascending aorta at baseline measured by target background ratio (TBR, normal ≥ 1.6) and week 15 using PET/CT. Secondary end point: CRP and serum lipids were calculated from baseline to week 16.	The study did not meet its primary end point but did show significant findings. Change at week 15 in mean max TBR improved with adalimumab compared with the control group both in the ascending aorta (p = .021) and in carotid arteries (p = .037), which showed decrease in vascular inflammation. hs-CRP levels were significantly decreased in the adalimumab group compared with those in the control group (p = .013). No statistically significant changes over time in serum lipids.	Small sample size of 30.

(continued)

TABLE 1. Summary of Primary Research Studies Reviewed on Biologic Therapy for Psoriasis Treatment, Continued

Author (Year), Country	Design Sample, Size	LOE	Intervention/IV	Outcomes measures/DV and Measures of outcome	Results	Limitations
Boehncke, Fichtlscherer, et al. (2011), Germany	Monocentric, prospective longitudinal observational study; 18–70 years old. *n* = 42 (only 25 completed the study; 17 were excluded because of nonadherence to dosing regimen).	4	Patients were assigned to one of the systemic antipsoriatic therapies approved in Germany: fumaric acid esters (*n* = 17), cyclosporine A (*n* = 2), methotrexate (*n* = 3), etanercept (*n* = 15), adalimumab (*n* = 4), or ustekinumab (*n* = 1).	Measures at baseline and at 12 and 24 weeks after systemic treatment. Outcome measures were correlation between reduction of the Psoriasis Area and Severity Index (PASI) and a change in high sensitivity C-reactive protein (hs-CRP)—biomarker for cardiac vascular risk. Secondary end points were correlations between a change of the PASI and vascular endothelial growth factor (VEGF), resistin, and adiponectin (metabolic factors reflecting insulin resistance).	Correlation of PASI and VEGF: total cohort, $p = .009$; with only responders (at least 50% PASI improvement), $p = .007$. Correlation of PASI and hs-CRP was not significant with the total cohort, $p = .08$, but was significant with just the responders, $p = .03$. Correlation of PASI and resistin with the responders seen ($p = .02$) as well as with PASI and adiponectin ($p = .007$).	The study was not powered to observe statistically significant differences with regard to the different therapeutics used. A limited number of patients were enrolled as well as a high dropout rate.
Jokai et al. (2013), Hungary	Consecutive cohort, *n* = 16 of patients with severe chronic plaque-type psoriasis: >15 PASI or >10% of body surface area.	4	TNF-alpha inhibitor agents (etanercept 3, infliximab 7, and adalimumab 6) were administered in standard doses accepted in the treatment of severe psoriasis vulgaris.	Difference between initial and 6-month intima-medial thickness (IMT) values was determined for monitored arteries collectively and separately in carotid and brachial arteries.	In the first group (13 of 16) without visible atherosclerosis, a significant decrease of IMT values, measured before starting therapy and at the end of the sixth month, was detected when involving all the followed arteries ($p = .0002$). Initial and follow-up data differed significantly also at individual analysis of carotid ($p = .011$) and brachial ($p = .006$) arteries. Nonstatistically significant trends were observed for a decrease in C-reactive protein from 5.99 to 3.36 mg/L ($p = .114$) and erythrocyte sedimentation rate from 18.11 to 10.06 mm/h ($p = .076$).	Small patient numbers, self-controlled study design, and lack of patients' stratification according to common cardiovascular risk factors.

(continued)

TABLE 1. Summary of Primary Research Studies Reviewed on Biologic Therapy for Psoriasis Treatment, Continued

Author (Year), Country	Design Sample, Size	LOE	Intervention/IV	Outcomes measures/DV and Measures of outcome	Results	Limitations
Strober et al. (2008), United States	Retrospective analysis from patients with psoriasis who participated in a randomized, double-blind, placebo-controlled, U.S. registration study; *n* = 652.	6	Retrospective secondary descriptive analysis of CRP levels measured in a previous RCT. Participants in the previous RCT were randomly assigned in a double-blinded fashion to receive either placebo or etanercept by subcutaneous injection for the first 12 weeks of this 24-week study.	Examines the effect of etanercept on CRP levels from baseline to week 12 compared with placebo.	Etanercept treatment reduced CRP levels significantly more than placebo treatment. After 12 weeks of treatment for patients with psoriasis without psoriatic arthritis ($p < .0001$). Patients with psoriasis with psoriatic arthritis were similar ($p < .001$). Placebo patients did not achieve reductions in CRP levels during the first 12 weeks.	Lack of verification of diagnosis of psoriatic arthritis; the exclusion of patients with certain comorbidities, such as congestive heart failure and insulin-dependent diabetes mellitus, which may have resulted in selection for patients with lower CRP levels.
Wu, Poon, and Bebchuk (2013), United States	Retrospective cohort study (January 1, 2004, to November 30, 2010); *n* = 8,845.	4	Data extracted from HealthConnect, the electronic database of Kaiser Permenente, Southern California, using three diagnosis codes for psoriasis. Each patient was assigned to one of three mutually exclusive cohorts as follows: *n* = 1,673 received TNF inhibitor for at least 2 months; *n* = 2,097 received oral agents or phototherapy cohort; and *n* = 5,075, no TNF inhibitors nor other systemic therapies or phototherapy but were treated with topical agents.	Incident MI (fatal or nonfatal)	Etanercept was associated with a significant reduction of MI risk, and monoclonal antibody and etanercept or monoclonal antibody were associated with a nonsignificant reduction of MI risk compared with topical agents.	Because the cohort reflects real-time clinical settings, many patients were given both etanercept as well as a monoclonal antibody TNF inhibitor over time. The lower number of patients in each subgroup of TNF inhibitors could lead to a lack of power that was unable to show a significant association of MI risk reduction.

Note. LOE = level of evidence; IV = independent variable; DV = dependent variable; MI = myocardial infarction; CRP = C-reactive protein; hs-CRP = highly sensitive CRP; ICD = International Classification of Diseases; PET/CT = positron emission tomography-computed tomography; RCT = randomized control trial; SQ = subcutaneous; TNF = tumor necrosis factor; UVB = ultra-violet B.

over time in serum lipid levels between the treatment groups, and Jokai et al. (2013) showed no statistically significant relationship of MI risk factors with CRP or sedimentation rate.

RECOMMENDATIONS AND CLINICAL IMPLICATIONS

Overall, the review of the research studies lends support to the positive effects of systemic treatment with biologics in reducing markers of inflammation. Treatment with biological agents or methotrexate in patients with severe psoriasis was associated with lower cardiovascular disease event rates compared with patients treated with other antipsoriatic therapies (Ahlehoff et al., 2013). This should be noted as a viable option to reduce cardiovascular morbidity and mortality. It also raises the question, as addressed by Boehncke, Salgo, et al. (2011), "Would early treatment with these systemic anti-inflammatory agents lead to possible prevention of developing these cardiovascular comorbidities?" Overall, there were several biomarkers such as decreased CRP levels that were improved with systemic or biologic therapy in patients with psoriasis. As stated by Wu et al. (2013), "It is too early to determine whether TNF inhibitors should be used in psoriasis patients specifically to reduce cardiovascular events. Results of a large prospective study may help determine this. Further, there are many new biologic agents currently on the market or coming onto the market, and there will be a need to understand the relationship between treatment with these agents and the risk of MI" (p. 902). The relationship should be highly considered and discussed with patients. Collaborative practice also needs to take place as psoriasis is not simply limited to the skin. Patients should be monitored for cardiovascular risk and also treated appropriately for these risks. As commonly seen, these studies suggest a need for additional research to confirm the results.

CONCLUSIONS

This review of research studies contributed to the understanding of an association of psoriasis to cardiovascular risk factors and that systemic treatment with biologic agents is starting to play a vital role in reducing this risk. Although additional research and evidence must be completed, the current evidence warrants a change in practice in the way patients with psoriasis are treated and managed. Efforts should be made to educate patients on their risks and risk management. Disseminating current research in regards to biologic agents and their role in decreasing cardiovascular risks in patients with psoriasis will help progress treatment protocols and enhance collaborative practice among providers. ■

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