

## Are drug treatments for psoriasis a cardiovascular risk?



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“Although randomized controlled trials are currently the gold-standard for measuring clinical efficacy in psoriasis therapies, these studies are designed to detect differences in the severity of psoriasis over short intervals, and as a result are underpowered to detect rare, serious or long-term adverse events.”

Multiple studies have shown psoriasis to be an independent risk factor for cardiovascular disease, particularly in patients with moderate-to-severe disease. Chronic, systemic inflammation is the proposed etiology for the increase in cardiovascular morbidity. Previous studies had suggested that the control of systemic inflammation with the use of methotrexate and antitumor necrosis factor agents had a cardioprotective effect in patients with psoriasis. While our recent meta-analysis of 22 randomized controlled trials (RCTs) did not show a statistically significant association between anti-IL-12/23 therapies and anti-TNF agents and major adverse cardiovascular events (MACE), the study had limited power to detect changes in rare events over a short period of time. Collection of comprehensive postmarketing safety data, and the use of observational pharmacoepidemiological studies plus drug registries will play an important role in addressing this limitation in addition to providing more conclusive data regarding the impact of established and future psoriasis therapies on cardiovascular events.

Psoriasis is a common autoimmune disease of cutaneous inflammation and keratinocyte hyperproliferation, manifesting clinically as scaly, raised, erythematous plaques. While the pathogenesis remains to be fully elucidated, a complex interplay between genetic and environmental influences is paramount in the development of the disease [1]. Recent studies have shown that patients with moderate-to-severe psoriasis have a clinically significant increased risk of cardiovascular disease together with cardiovascular risk factors such as Type 2 diabetes mellitus, obesity, smoking and the metabolic syndrome compared to the general population, with an overall increase in all-cause mortality [2]. The mechanistic link between psoriasis and this observed increase in cardiovascular comorbidities has not been fully defined. It is clear, however, that common inflammatory pathways are at play in the pathophysiology of psoriasis, obesity and coronary artery disease.

### Cardiovascular risk in psoriasis patients

The association of psoriasis with cardiovascular disease was first observed almost 40 years ago

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“...until more definitive data become available, dermatologists should exercise heightened vigilance for cardiovascular risk factors when initiating anti-IL-12/23 agents in psoriasis patients.”

[3], but only in recent times has this become recognized as an important comorbidity of psoriasis. A prospective, population-based cohort study using the GP Database in the UK compared outcomes in patients with psoriasis to those without the disease [2]. A total of 556,995 control patients, 127,139 patients with mild psoriasis and 3837 patients with severe psoriasis were identified. Patients with psoriasis had an increased adjusted relative risk for myocardial infarction, after controlling for other cardiovascular risk factors. The relative risk was greatest in young patients with severe psoriasis, approaching a threefold increase in the risk of myocardial infarction for male psoriasis patients at the age of 30 years. Other studies have also shown an increase in cardiovascular disease, peripheral vascular disease, stroke and overall mortality [4–6]. The risk of cardiovascular morbidity and mortality appear to be higher in those with more severe psoriasis [4,6]. Another study using the UK GP Database calculated the incidence of risk factors for cardiovascular disease, including incident diabetes, hypertension, obesity and hyperlipidemia after a first recorded diagnosis of psoriasis [5]. Hazard ratios for these conditions were increased in psoriasis patients compared with the general population.

#### Impact of systemic treatment on cardiovascular risk in psoriasis patients: an overview of studies to date

It has been proposed that control of systemic inflammation in chronic inflammatory disorders could help reduce cardiovascular morbidity. Indeed, a cardioprotective effect has been shown with systemic agents such as methotrexate and anti-TNF- $\alpha$  agents in rheumatoid arthritis (RA) and psoriasis populations [7]. In a retrospective cohort study of 7615 psoriasis patients and 6707 RA patients at the Veterans Integrated Service network the effect of methotrexate on cardiovascular events was evaluated. Methotrexate significantly reduced the risk of vascular disease compared to those who were not treated with methotrexate (odds ratio of 0.73 and 0.83 for psoriasis and RA, respectively). This reduction was most evident in patients receiving a low cumulative dose of methotrexate and was reduced further by the concomitant use of folic acid.

Boehncke *et al.* showed an increase in the protective cytokine adiponectin and a

reduction in circulating CRP following treatment of psoriasis with fumaric acid esters [8]. Similarly, another study by the same authors showed a favorable effect of continuous systemic treatment for psoriasis on biomarkers for cardiovascular risk [9].

More recently, the Kaiser Permanente health-care database in California (USA) was used to conduct a retrospective cohort study of 24,081 psoriasis patients examining the effect of TNF inhibitors ( $n = 2463$ ) on the incidence of myocardial infarction [10]. A multivariate analysis was performed to control for cardiovascular risk factors. The use of TNF- $\alpha$  inhibitors reduced the risk of myocardial infarction by 48% ( $p = 0.0062$ ). The presence of severe disease, psoriatic arthritis, diabetes mellitus, hypertension and dyslipidemia increased the risk of myocardial infarction in the univariate analysis, while females and patients under the age of 65 years had a decreased risk. Of note, the use of methotrexate, smoking and increased BMI were not associated with the risk of myocardial infarction.

A study evaluating the effect of etanercept, a TNF- $\alpha$  inhibitor, on inflammatory biomarkers in psoriasis, showed a significant decrease in CRP in psoriasis and psoriatic arthritis patients [11]. Another study of 41 patients also showed a significant decrease in the frequency of white blood cells and neutrophils, fibrinogen, ferritin, hs-CRP, erythrocyte sedimentation rate, haptoglobin, ceruloplasmin and  $\alpha$ 1-antitrypsin after treatment with etanercept. The severity of psoriasis, as measured by psoriasis area and severity index, correlated with fibrinogen and hs-CRP [12].

A randomized, placebo-controlled study of 127 patients with psoriatic arthritis and active psoriasis studied the effect of onerecept (a recombinant human TNF- $\alpha$  binding protein 1) on cardiovascular risk factors including concentrations of lipids, lipoproteins, Apo A1, Apo B, lipoprotein a, ICAM-1, homocysteine and SHBG (a surrogate marker of insulin resistance) [13]. Onerecept significantly reduced the levels of CRP, lipoprotein A and homocysteine and increased the level of SHBG.

More recently there was concern regarding preliminary reports of a numerical excess of MACE in RCTs of psoriasis patients treated with ustekinumab (Centocor) and briakinumab (Abbott), both of which are highly effective

monoclonal antibodies against the p40 subunit common to IL-12 and IL-23 [14–22]. There were 10 MACE in anti-IL-12/23-treated patients in the placebo-controlled phases of Phase II and III studies of ustekinumab (n = 5) and briakinumab (n = 5) compared to zero events in placebo-treated patients, and a paucity of events reported from studies of anti-TNF- $\alpha$ -treated psoriasis patients with similar disease severity. A total of 61 MACE have occurred to date across all phases of these anti-IL-12/23 studies; 34 MACE, including one cardiovascular death occurred in studies of ustekinumab and 27 MACE, including four cardiovascular deaths, in studies of briakinumab.

In order to evaluate a potential association between biologics and MACE, we conducted an independent meta-analysis of 22 RCTs comprising 10,183 patients [23]. During the placebo-controlled phases of the anti-IL-12/23 studies, ten of the 3179 patients treated with anti-IL-12/23 therapies had a MACE compared with zero events in 1474 patients treated with placebo (Mantel Haenszel [MH] risk difference 0.012 events/patient years, 95% CI: -0.001–0.026; p = 0.12). In anti-TNF- $\alpha$  trials, only one of 3858 patients treated with anti-TNF- $\alpha$  treatments had a MACE compared with one of 1812 treated with placebo (MH risk difference 0.0005 events/patient years, 95% CI: -0.010–0.009; p = 0.94). Although there was no significant difference in the rate of MACE observed with patients receiving anti-IL-12/IL-23 antibody or anti-TNF- $\alpha$  treatments compared with placebo, the findings did raise questions about the cardiovascular safety of the anti-IL-12/23 agents. After identification of these cases, the manufacturers of briakinumab performed a statistical analysis to determine whether a specific subset of treated patients may be at particularly high risk of a MACE. This analysis resulted in an amendment to the study protocol for the open-label continuation phase of this study to adjust the exclusion criteria, visit procedures and discontinuation criteria for enrolled patients. Patients with two or more predefined cardiovascular risk factors, who had not previously experienced failure or intolerance to anti-TNF- $\alpha$  or systemic therapies, were withdrawn from the study. Subsequently, Abbott discontinued all clinical trials involving briakinumab pending further research into these cardiovascular issues. We therefore believe that until more definitive

data become available, dermatologists should exercise heightened vigilance for cardiovascular risk factors when initiating anti-IL-12/23 agents in psoriasis patients.

One of the most important conclusions of our meta-analysis, however, was the limited ability of placebo-controlled clinical trials to reliably interpret the significance of rare events given their current design. Although RCTs are currently the gold-standard for measuring clinical efficacy in psoriasis therapies, these studies are designed to detect differences in the severity of psoriasis over short intervals, and as a result are underpowered to detect rare, serious or long-term adverse events. For example, in our meta-analysis, a sample size of 4284 patient-years would be required to demonstrate a 0.5% absolute increase in the frequency of MACE with 80% power during the placebo-controlled phase using the typical 2:1, biologic treatment:placebo study design based on a background rate of 0.0012 events/patient-years (events/patient years; aggregate rate in the placebo arm of all 22 studies). A systematic strategy needs to be implemented across RCTs of all new psoriasis therapies to screen, capture and adjudicate cardiovascular events. Numerous new systemic and biologic treatments are currently in development. It is essential that the effect of these agents on vascular inflammation be fully explored with more intense evaluations than have been carried out so far. These further studies could include the use of appropriate imaging, assessments of endothelial function and carefully selected biomarkers of cardiovascular risk in prospective clinical trials *inter alia*.

### Conclusion

There is growing evidence to support the beneficial effect of systemic treatment on cardiovascular risk, particularly with regard to methotrexate and anti-TNF- $\alpha$  treatments in the psoriatic and RA populations. By contrast, our recent meta-analysis suggests a potential association between anti-IL-12/23 agents and cardiovascular risk. Larger, long-term studies are essential to further examine this association. The short time-frame (approximately weeks on average) of current placebo-controlled phases greatly hinders the statistical power to make conclusions regarding safety, particularly concerning rare events, such as cardiovascular events and malignancy. Thus,

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despite revolutionary advances in the therapy of psoriasis, long-term experience of newer, targeted agents is still limited and robust evidence of long-term safety is still an absolute necessity. Phased approval, mandating the continued collection of comprehensive safety data in postmarketing and observational pharmacoepidemiological studies will hopefully address this important need [24]. The use of carefully constructed registries is also essential to monitor the longer term safety of new agents under development, particularly relating to cardiovascular risk in the psoriasis population.

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**References**

- 1 Nestle FO, Kaplan DH, Barker J. Psoriasis. *N. Engl. J. Med.* 361(5), 496–509 (2009).
- 2 Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. *JAMA* 296(14), 1735–1741 (2006).
- 3 McDonald CJ, Calabresi P. Occlusive vascular disease in psoriatic patients. *N. Engl. J. Med.* 288(17), 912 (1973).
- 4 Gelfand JM, Troxel AB, Lewis JD *et al.* The risk of mortality in patients with psoriasis: results from a population-based study. *Arch. Dermatol.* 143(12), 1493–1499 (2007).
- 5 Kaye JA, Li L, Jick SS. Incidence of risk factors for myocardial infarction and other vascular diseases in patients with psoriasis. *Br. J. Dermatol.* 159(4), 895–902 (2008).
- 6 Mallbris L, Akre O, Granath F *et al.* Increased risk for cardiovascular mortality in psoriasis inpatients but not in outpatients. *Eur. J. Epidemiol.* 19(3), 225–230 (2004).
- 7 Prodanovich S, Prodanowich S, Ma F *et al.* Methotrexate reduces incidence of vascular diseases in veterans with psoriasis or rheumatoid arthritis. *J. Am. Acad. Dermatol.* 52(2), 262–267 (2005).
- 8 Boehncke S, Fichtlscherer S, Salgo R *et al.* Systemic therapy of plaque-type psoriasis ameliorates endothelial cell function: results of a prospective longitudinal pilot trial. *Arch. Dermatol. Res.* 303(6), 381–388 (2011).
- 9 Boehncke S, Salgo R, Garbaraviciene J *et al.* Effective continuous systemic therapy of severe plaque-type psoriasis is accompanied by amelioration of biomarkers of cardiovascular risk: results of a prospective longitudinal observational study. *J. Eur. Acad. Dermatol. Venereol.* 25(10), 1187–1193 (2011).
- 10 Wu J, Fisher A, Poon K, Burchette R, Shen A. The effect of tumor necrosis factor- $\alpha$  inhibitors on the risk of myocardial infarction in patients with psoriasis. Presented at: *Annual Meeting of the American Academy of Dermatology*. New Orleans, LA, USA, 4–8 February 2011.
- 11 Strober B, Teller C, Yamauchi P *et al.* Effects of etanercept on C-reactive protein levels in psoriasis and psoriatic arthritis. *Br. J. Dermatol.* 159(2), 322–330 (2008).
- 12 Kanelleas A, Liapi C, Katoulis A *et al.* The role of inflammatory markers in assessing disease severity and response to treatment in patients with psoriasis treated with etanercept. *Clin. Exp. Dermatol.* 36(8), 845–850 (2011).
- 13 Sattar N, Crompton P, Cherry L, Kane D, Lowe G, McInnes IB. Effects of tumor necrosis factor blockade on cardiovascular risk factors in psoriatic arthritis: a double-blind, placebo-controlled study. *Arthritis Rheum.* 56(3), 831–839 (2007).
- 14 Leonardi CL, Kimball AB, Papp KA *et al.* Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 371(9625), 1665–1674 (2008).
- 15 Papp KA, Langley RG, Lebwohl M *et al.* Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 371(9625), 1675–1684 (2008).
- 16 Krueger GG, Langley RG, Leonardi C *et al.* A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. *N. Engl. J. Med.* 356(6), 580–592 (2007).
- 17 Tsai TF, Ho JC, Song M *et al.* Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: a Phase 3, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL). *J. Dermatol. Sci.* 63(3), 154–163 (2011).
- 18 Igarashi A, Kato T, Kato M, Nakagawa H. A randomized, double-blind, placebo-controlled study of ustekinumab in Japanese patients with moderate to severe plaque psoriasis. Presented at: *Congress of the Psoriasis International Network*, Paris, France 1 July 2010 (Abstract).
- 19 Kimball AB, Gordon KB, Langley RG *et al.* Safety and efficacy of ABT-874, a fully human interleukin 12/23 monoclonal antibody, in the treatment of moderate to severe chronic plaque psoriasis: results of a randomized, placebo-controlled, Phase 2 trial. *Arch. Dermatol.* 144(2), 200–207 (2008).

- 20 Strober BE, Crowley JJ, Yamauchi PS, Olds M, Williams DA. Efficacy and safety results from a Phase 3, randomized controlled trial comparing the safety and efficacy of briakinumab with etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. *Br. J. Dermatol.* 165(3), 661–668 (2011).
- 21 Gottlieb AB, Leonardi C, Kerdel F, Mehlis S, Olds M, Williams DA. Efficacy and safety of briakinumab vs. etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. *Br. J. Dermatol.* 165(3), 652–660 (2011).
- 22 Gordon K, Langley R, Gottlieb A *et al.* A Phase III, randomized controlled trial of the fully human IL-12/23 monoclonal antibody, briakinumab, in moderate-to-severe psoriasis. *J. Invest. Dermatol.* doi:10.1038/jid.2011.304 (2011) (Epub ahead of print).
- 23 Ryan C, Leonardi CL, Krueger JG *et al.* Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: a meta-analysis of randomized controlled trials. *JAMA* 306(8), 864–871 (2011).
- 24 Strom BL. How the US drug safety system should be changed. *JAMA* 295(17), 2072–2075 (2006).