Impact of Secukinumab on Endothelial Dysfunction and Other Cardiovascular Disease Parameters in Psoriasis Patients over 52 Weeks

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Psoriasis increases the risk of cardiovascular (CV) disease. Secukinumab, a fully human monoclonal antibody against IL-17A, shows significant efficacy in psoriasis, but effects on CV markers are unknown. CARIMA (Evaluation of Cardiovascular Risk Markers in Psoriasis Patients Treated with Secukinumab) was a 52-week, randomized, double-blind, placebo-controlled, exploratory trial in patients with moderate to severe plaque psoriasis without clinical CV disease. Patients were randomly assigned to receive 300 mg or 150 mg secukinumab until week 52 or to receive placebo until week 12 and then 300 mg or 150 mg secukinumab until week 52. The primary outcome was endothelial function measured by flow-mediated dilation (FMD). Baseline FMD was significantly lower in psoriasis patients than healthy volunteers (4.4 ± 3.9% vs. 6.1 ± 3.3%, P = 0.01). At week 12, baseline-adjusted mean FMD was numerically higher in patients receiving secukinumab versus those receiving placebo, but this difference (300-mg group, +1.2%; 150-mg group, +0.76%; P = 0.223 and P = 0.403 by analysis of covariance) did not reach significance. At week 52, FMD increased across groups. FMD was significantly higher than baseline in patients receiving the label dose of 300 mg secukinumab for 52 weeks (+2.1%, 95% confidence interval = 0.8–3.3; P = 0.0022). Other relevant CV markers were unchanged. CARIMA indicates that secukinumab might have a beneficial effect on CV risk by improving the endothelial function of patients with plaque psoriasis.


INTRODUCTION

Plaque psoriasis is a chronic immune-mediated disease characterized by skin and/or joint manifestations and systemic inflammation (Dowlatshahi et al., 2013). Psoriasis is independently associated with cardiovascular (CV) comorbidity (Augustin et al., 2010b; Gelfand et al., 2006; Mehta et al., 2010) and is also associated with a higher prevalence of metabolic syndrome, diabetes, and hyperlipidemia (Augustin et al., 2010b). The etiology of this association is unknown, but low-grade systemic inflammation may promote vascular injury, leading to enhanced CV risk, as recently reviewed in by Puig (2018) and Boehncke (2018). Psoriasis has been linked to vascular inflammation and to the presence of neutrophils and systemic biomarkers of inflammation (Mehta et al., 2011; Naik et al., 2015). Psoriasis severity is associated with CV risk, with a 3-fold increased risk observed in patients with severe psoriasis compared with healthy control individuals (Gelfand et al., 2006). Coronary artery plaque burden was also increased in patients with severe psoriasis (Hjuler et al., 2015; Ludwig et al., 2007), and high-risk, rupture-prone coronary artery plaques were shown to be increased with psoriasis (Lerman et al., 2017).

There are limited systematic data evaluating how biologic therapy may affect CV risk in psoriasis patients. The use of anti-tumor necrosis factor-alpha (TNF-α) agents in rheumatoid arthritis patients was shown to reduce the risk of major
adverse CV events over 8 years (Wu et al., 2017), but no similar study exists for psoriasis therapies to date. In psoriasis patients, however, improved skin disease was correlated with improvement in aortic vascular inflammation as measured by 18F-fluorodeoxyglucose positron emission tomography/computed tomography after 1 year of anti-TNF-α treatment (Dey et al., 2017).

Secukinumab is a fully human monoclonal antibody that selectively neutralizes IL-17A, a key cytokine involved in the development of psoriasis (Zeichner and Armstrong, 2016). Secukinumab has shown long-lasting efficacy and safety in the complete spectrum of psoriasis manifestations, including nails, scalp, palms and soles, and psoriatic arthritis (Baeten et al., 2013; Langley et al., 2014; McInnes et al., 2015; Thaci et al., 2015). Given the efficacy of secukinumab on skin manifestations and the lack of available data on the effect of anti-IL-17A on CV risk markers in psoriasis, CARIMA (Evaluation of Cardiovascular Risk Markers in Psoriasis Patients Treated with Secukinumab) (NCT02559622) was designed to explore the effects of secukinumab on CV risk markers in patients with psoriasis. Flow-mediated dilation (FMD), a measure of endothelium-dependent control of vascular tone, was assessed as a parameter of vascular endothelial function and early predictor of CV prognosis. Previous studies showed that a 1% increase in FMD correlates with an approximately 13% decrease in relative CV risk (Inaba et al., 2010). Arterial stiffness, various blood biomarkers, and plaque burden by magnetic resonance imaging (MRI) were also assessed.

RESULTS
Patients
A total of 151 patients were recruited after screening. The full analysis set FAS comprised 48 patients in group A (secukinumab 300 mg), 54 in group B (secukinumab 150 mg), 26 in group C (placebo-secukinumab 300 mg), and 23 in group D (placebo-secukinumab 150 mg) (see Supplementary Figure S1 online). There were 11 discontinuations during the study period, with adverse events the most common reason for discontinuation (n = 6) (see Supplementary Figure S1). Baseline participant characteristics were balanced among treatment groups (Table 1). Between 15% and 28% of patients in each group had concomitant psoriatic arthritis (Table 1). A high proportion of patients (~40%) were current smokers at baseline (Table 1).

Psoriasis Area and Severity Index response
Psoriasis Area and Severity Index (PASI) response rates for the secukinumab arms were similar to those reported in previous phase 3 clinical trials (Langley et al., 2014). At week 12, 81.3% of patients treated with secukinumab 300 mg achieved a response of 75% reduction in PASI score, and 56.3% reached a 90% reduction in PASI score, compared with 0% who received placebo. At week 52, 81.3% patients treated with secukinumab 300 mg reached a 75% reduction in PASI score, and 60.4% reached a 90% reduction in PASI score. No relevant correlations between PASI response, vascular changes, or CV biomarkers were observed.

Flow-mediated dilation
FMD repeatability assessments are described in the Supplementary Materials online. Pooled mean baseline FMD was 4.4% ± 3.9% in all psoriasis patients, compared with a mean FMD of 6.1% ± 3.3% measured in a group of 49 volunteers without psoriasis during site training (P = 0.01) (Figure 1); non–psoriasis-related health status of the volunteers was unknown. At week 12, FMD increased to 5.1% ± 5.2% in the 300-mg group and 4.8% ± 3.9% in the 150-mg group (Table 2), both without a significant baseline-adjusted

Table 1. Baseline demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>A. Secukinumab 300 mg (n = 48)</th>
<th>B. Secukinumab 150 mg (n = 54)</th>
<th>C. Placebo/Secukinumab 300 mg (n = 26)</th>
<th>D. Placebo/Secukinumab 150 mg (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>44.2 (12.9)</td>
<td>46.0 (14.4)</td>
<td>43.7 (11.4)</td>
<td>46.8 (13.1)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>37 (77.1)</td>
<td>31 (57.4)</td>
<td>18 (69.2)</td>
<td>16 (69.6)</td>
</tr>
<tr>
<td>Body weight in kg, mean (SD)</td>
<td>86.5 (15.3)</td>
<td>84.4 (19.3)</td>
<td>95.4 (26.0)</td>
<td>89.8 (22.0)</td>
</tr>
<tr>
<td>Mean BMI, kg/m²</td>
<td>27.8</td>
<td>28.1</td>
<td>30.1</td>
<td>29.7</td>
</tr>
<tr>
<td>Baseline PASI, mean (SD)</td>
<td>19.3 (7.9)</td>
<td>21.7 (10.5)</td>
<td>17.5 (4.2)</td>
<td>19.5 (6.1)</td>
</tr>
<tr>
<td>Time since psoriasis diagnosis, mean (SD)</td>
<td>20.6 (12.7)</td>
<td>20.8 (13.3)</td>
<td>18.9 (11.7)</td>
<td>20.3 (11.7)</td>
</tr>
<tr>
<td>Psoriatic arthritis present, n (%)</td>
<td>12 (25.0)</td>
<td>15 (27.8)</td>
<td>4 (15.4)</td>
<td>4 (17.4)</td>
</tr>
<tr>
<td>Prior nonbiologic systemic therapy, n (%)</td>
<td>43 (89.6)</td>
<td>46 (85.2)</td>
<td>24 (92.3)</td>
<td>16 (69.6)</td>
</tr>
<tr>
<td>Prior biologic systemic therapy, n (%)</td>
<td>15 (31.3)</td>
<td>20 (37.0)</td>
<td>8 (30.8)</td>
<td>9 (39.1)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>4 (8.3)</td>
<td>9 (16.7)</td>
<td>3 (11.5)</td>
<td>—</td>
</tr>
<tr>
<td>Dyslipidemia/Hyperlipidemia, n (%)</td>
<td>3 (6.3)</td>
<td>3 (5.6)</td>
<td>5 (19.2)</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>13 (27.1)</td>
<td>14 (25.9)</td>
<td>9 (34.6)</td>
<td>7 (30.4)</td>
</tr>
<tr>
<td>Other coronary artery disease, n (%)</td>
<td>1 (2.1)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Prior stroke: unknown type, n (%)</td>
<td>1 (2.1)</td>
<td>—</td>
<td>1 (3.8)</td>
<td>—</td>
</tr>
<tr>
<td>Pulmonary embolism, n (%)</td>
<td>—</td>
<td>1 (1.9)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Supraventricular tachycardia, n (%)</td>
<td>—</td>
<td>1 (1.9)</td>
<td>1 (3.8)</td>
<td>—</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td>Never</td>
<td>19 (39.6)</td>
<td>21 (38.9)</td>
<td>11 (42.3)</td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>9 (18.8)</td>
<td>11 (20.4)</td>
<td>3 (11.5)</td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>20 (41.7)</td>
<td>22 (40.7)</td>
<td>12 (46.2)</td>
</tr>
</tbody>
</table>

BMI, body mass index; PASI, psoriasis area and severity index; SD, standard deviation
difference compared with the pooled mean (3.65% ± 4.07%) in the placebo groups (+1.2%, \( P = 0.223 \) vs. 300 mg and +0.76%, \( P = 0.403 \) vs. 150 mg by analysis of covariance). At week 52, FMD had increased to a mean of 6.3% ± 4.6% in patients treated with secukinumab 300 mg and to 6.0% ± 4.2% in those receiving secukinumab 150 mg (Table 2). FMD was significantly improved compared with baseline in the group of patients treated with the label dose of secukinumab 300 mg for 52 weeks (change in FMD from baseline = +2.1%, 95% confidence interval [CI] = 0.8–3.3; \( P = 0.0022 \)) (Table 2 and Figure 2). A similar change was observed in the group who received secukinumab 150 mg (change from baseline: +2.1%, 95% CI = 0.7–3.4; \( P = 0.0034 \)) (Figure 2) for 52 weeks. In the group of participants who received placebo for 12 weeks followed by secukinumab 150 mg for 40 weeks, the change in FMD from baseline was smaller (+1.2%, 95% CI = −1.0 to 3.5) and did not reach statistical significance \( (P = 0.2538) \). Similar observations were made when the analysis was performed in the per-protocol population.

When various subgroups were analyzed by sex, smoking status, or Framingham risk score, there were no consistent differences in FMD between groups, but higher increases in FMD were seen at week 52 than week 12 (see Supplementary Table S1 online). When FMD was analyzed by response subgroups, no clear pattern of difference emerged for secukinumab 300 mg- and 150 mg-treated patients at week 12 and week 52 (see Supplementary Tables S2 and S3 online).

There were no significant correlations between PASI score and FMD at baseline for the full analysis set (Pearson coefficient = 0.068, \( P = 0.436 \)) or for patients with PASI score greater than 20 (Pearson coefficient = 0.122, \( P = 0.388 \)). In addition, no significant correlation was observed between PASI and FMD at week 12 after secukinumab treatment (see Supplementary Figure S2 online).

### Arterial stiffness

Pooled baseline augmentation index was 24.8% ± 11.0% (mean ± standard deviation; normal range for men aged 40–49 years = 19% ± 10% and for women aged 40–49 years = 28% ± 10% [Janner et al., 2010]). Baseline pooled pulse wave velocity (PWV) was 7.9 ± 1.9 m/s (mean ± standard deviation; normal range [age dependent] = 6.2 [<30 years] to 10.9 [≥70 years] [The Reference Values for Arterial Stiffness’ Collaboration, 2010]). No clinically relevant changes were observed in the study. Mean absolute changes in augmentation index and PWV between patients treated with secukinumab 300 mg versus placebo at week 12, and between secukinumab 300 mg-treated patients at week 52 versus baseline, were not statistically significant (see Supplementary Table S4 online).

### MRI of vessel walls

The MRI substudy assessed the total plaque burden in the carotid artery and the aorta measured from assessment of the vessel wall area in 40 patients. No consistent clinically relevant changes in any of the MRI parameters were observed during the study, either from baseline or at any treatment time point (see Supplementary Table S5 online). Normalized wall index values are consistent with some vessel wall thickening due to early inflammation, but none of the participants had presence of complex plaques (see Supplementary Table S5).

### Soluble markers of systemic inflammation and lipid and glucose metabolism

Data for serum biomarkers of inflammation and metabolism are shown in Table 3. Most measured parameters were within normal ranges at baseline (Table 3). For these parameters, no

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**Table 2. Flow-mediated dilation to week 12 and week 52**

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Secukinumab 300 mg (n = 48)</th>
<th>Secukinumab 150 mg (n = 54)</th>
<th>Placebo-Secukinumab 300 mg (n = 26)</th>
<th>Placebo-Secukinumab 150 mg (n = 23)</th>
<th>Mean Absolute Change in FMD Compared with Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>4.6 ± 3.5</td>
<td>4.6 ± 3.6</td>
<td>3.9 ± 3.9</td>
<td>3.7 ± 3.2</td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>5.1 ± 5.2(^1)</td>
<td>4.8 ± 3.9</td>
<td>3.6 ± 3.7</td>
<td>3.6 ± 4.6</td>
<td>2.13 (0.8, 3.3)</td>
</tr>
<tr>
<td>Week 52</td>
<td>6.3 ± 4.6</td>
<td>6.0 ± 4.2</td>
<td>6.4 ± 4.8</td>
<td>4.8 ± 3.3</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: FMD, flow-mediated dilation; SD, standard deviation.

\(^1\)Reference value expected in healthy individuals: 7%–10% (Ghiadoni et al., 2012; Moens et al., 2005).

\(^2\)Primary endpoint: baseline-adjusted mean absolute change in FMD compared with pooled placebo groups = 1.17% (95% confidence interval = −0.1 to 3.1), \( P = 0.223 \).

\(^3\)Baseline-adjusted mean absolute change in FMD compared with baseline = 2.1% (95% confidence interval = 0.8–3.3), \( P = 0.0022 \).
consistent clinically relevant changes were observed during the study. High-sensitivity C reactive protein level and homeostatic model assessment insulin resistance were elevated at baseline, indicating low-grade systemic inflammation and insulin resistance (Table 3). At week 12, there were no significant differences in these parameters between secukinumab 300 mg and the pooled placebo group (Table 3), nor were significant decreases observed at week 52 compared with baseline (Table 3). A significant decrease in adiponectin was seen at week 12 in the secukinumab-treated groups versus the placebo group, and a significant decrease in homeostatic model assessment insulin resistance were observed after treatment. This may be a result of the selection of a psoriasis patient population without pre-existing indicators of CV disease.

**DISCUSSION**

The CARIMA study evaluated CV risk markers in patients with moderate to severe plaque psoriasis treated with secukinumab for 1 year. The primary objective of FMD improvement at week 12 with secukinumab 300 mg (label dose) versus placebo was not met, although a dose-dependent clinically relevant improvement in FMD was observed (1.2%). At week 52, a significant increase in absolute FMD of 2.1% was seen compared with baseline in patients treated with secukinumab 300 mg. No proatherogenic changes in blood biomarkers or indicators of vessel wall function and morphology (arterial stiffness, MRI) were observed after treatment. This may be a result of the selection of a psoriasis patient population without pre-existing indicators of CV disease.

Studies of the effects of biologic treatments for inflammatory disorders on FMD have been limited to date. Improvement in FMD was seen in 14 patients with psoriasis treated with adalimumab in a small study (Avgerinou et al., 2011). Patients treated with infliximab and etanercept showed
changes in FMD and baseline readings varied widely between arthritis patients (Ramonda et al., 2014). The absolute increase at month 12 was also observed in 34 rheumatoid arthritis patients treated with adalimumab (Gonzalez-Juanatey et al., 2012). Conversely, no recovery in FMD was observed after 2 years of anti-TNF-α treatment in 32 psoriatic arthritis patients (Maggio et al., 2008). The absolute changes in FMD and baseline readings varied widely between studies.

Confirming earlier findings of endothelial dysfunction associated with subclinical atherosclerosis in psoriasis patients, significantly lower mean baseline FMD was observed in psoriasis patients than in volunteers without psoriasis. An increase in FMD was observed in all treated groups at 52 weeks. A time point of 12 weeks was chosen because at this point improvements in the skin become evident with secukinumab; however, improvements in FMD occurred at a later point, which suggests that changes in the vessel wall and endothelial function occur later than those observed in the skin. When put in the perspective of larger cohort studies, the increase in FMD at week 52 may indeed be clinically relevant, given that a 1% increase in absolute FMD is associated with a 13% decrease in relative CV risk in one study (Inaba et al., 2010).

Table 3. Changes in soluble biomarkers at week 12 and week 52

<table>
<thead>
<tr>
<th>Soluble Biomarker</th>
<th>Normal Values/Range</th>
<th>Pooled Baseline Mean Value (A + B + C + D)</th>
<th>Mean (95% CI) Difference in Values at Week 12 Between Secukinumab 300 mg and Pooled Placebo: A Compared with C + D</th>
<th>Mean (95% CI) Difference in Values for Secukinumab 300 mg at Week 52 (A) Compared with Baseline (A)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inflammatory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S100B protein, µg/L (n = 147)</td>
<td>&lt;0.15 (Thelin et al. 2017)</td>
<td>0.06</td>
<td>0.02** (−0.03 to −0.01)</td>
<td>0.0</td>
</tr>
<tr>
<td>HS-CRP, mg/dl (n = 144)</td>
<td>0.3 (Adeli et al. 2015)</td>
<td>0.6</td>
<td>0.04 (−0.3 to 0.4)</td>
<td>−0.1 (−0.3 to 0.1)</td>
</tr>
<tr>
<td><strong>Lipid</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apolipoprotein A1, mg/dl (n = 144)</td>
<td>≥120 (Adeli et al. 2015)</td>
<td>161.6</td>
<td>0.5 (−6.6 to 7.7)</td>
<td>−4.5 (−10.0 to 0.9)</td>
</tr>
<tr>
<td>Apolipoprotein B in mg/dl (n = 144)</td>
<td>40–125 (Adeli et al. 2015)</td>
<td>106.1</td>
<td>−0.02 (−5.0 to 5.0)</td>
<td>3.7 (−2.2 to 9.6)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl (n = 144)</td>
<td>≥60 (Grundy et al. 2014)</td>
<td>51.9</td>
<td>−0.8 (−3.6 to 2.1)</td>
<td>0.1 (−2.1 to 2.4)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl (n = 144)</td>
<td>&lt;100 (Grundy et al. 2014)</td>
<td>138.4</td>
<td>0.2 (−8.4 to 8.7)</td>
<td>1.7 (−6.5 to 9.9)</td>
</tr>
<tr>
<td>Adiponectin, µg/ml (n = 147)</td>
<td>4–37, sex and weight dependent</td>
<td>6.9</td>
<td>−0.9* (−1.6 to −0.2)</td>
<td>−1.1** (−1.6 to −0.6)</td>
</tr>
<tr>
<td>Leptin, ng/ml (n = 147)</td>
<td>Males: 0.7–5.3 Females: 3.3–18.3 (Gijón-Conde et al. 2015)</td>
<td>8.7</td>
<td>0.3 (−1.2 to 1.7)</td>
<td>0.2 (−1.0 to 1.3)</td>
</tr>
<tr>
<td>Cholesterol, mg/dl (n = 144)</td>
<td>&lt;200 (Grundy et al. 2014)</td>
<td>203.1</td>
<td>−0.8 (−10.1 to 8.5)</td>
<td>7.8* (0.0 to 15.6)</td>
</tr>
<tr>
<td>Triglycerides, mg/dl (n = 144)</td>
<td>&lt;150 (Grundy et al. 2014)</td>
<td>132.8</td>
<td>−24.0* (−45.0 to −3.0)</td>
<td>64.6 (−44.0 to 173.2)</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose, mg/dl (n = 145)</td>
<td>&lt;100 American Diabetes Association (n = 140)</td>
<td>95.5</td>
<td>1.9 (−4.4 to 8.2)</td>
<td>−0.8 (−3.5 to 2.0)</td>
</tr>
<tr>
<td>HOMA insulin resistance (index)</td>
<td>(n = 140)</td>
<td>—</td>
<td>−0.2 (−2.0 to 1.7)</td>
<td>−0.2 (−1.2 to 0.9)</td>
</tr>
<tr>
<td>HOMA β-cell function, %</td>
<td>(n = 140)</td>
<td>—</td>
<td>−11.3 (−68.3 to 45.8)</td>
<td>11.5 (−40.5 to 63.5)</td>
</tr>
<tr>
<td>Insulin, µIU/ml (n = 147)</td>
<td>&lt;25 (Adeli et al. 2015)</td>
<td>14.9</td>
<td>−1.2 (−5.7 to 3.3)</td>
<td>−0.4 (−4.3 to 3.6)</td>
</tr>
<tr>
<td>SHBG, nmol/L (n = 144)</td>
<td>10–57 (Maggio et al. 2008)</td>
<td>48.6</td>
<td>−3.7 (−8.2 to 0.8)</td>
<td>−3.1 (−10.8 to 4.6)</td>
</tr>
<tr>
<td>HbA1C absolute, mmol/mol Hb</td>
<td>(n = 146)</td>
<td>&lt;42 (Adeli et al. 2015)</td>
<td>38.1</td>
<td>0.5 (−1.2 to 2.2)</td>
</tr>
</tbody>
</table>

Abbreviations: A, secukinumab 300 mg group; B, secukinumab 150 mg group; C, placebo/secukinumab 300 mg group; CI, confidence interval; D, placebo/secukinumab 150 mg group; Hb, hemoglobin; HDL, high density lipoprotein; HOMA, homeostatic model assessment; HS-CRP, high-sensitivity C reactive protein; LDL, low density lipoprotein; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; SD, standard deviation; SHBG, sex hormone-binding globulin.

1 Numbers are for the sum of evaluable patients across groups A, B, C, and D.
2 Reference values expected in healthy individuals.
*P < 0.05. **P < 0.005.
in volunteers without psoriasis at baseline. Other secondary parameters of vascular structure (e.g., MRI) and function (e.g., PWV) were normal at baseline and showed no significant changes during the course of the study. Increased coronary artery plaque burden has been observed in psoriasis patients (Lerman et al., 2017), but no changes were detected in vessel wall thickness or plaque area in CARIMA. Collectively, these data suggest that secukinumab has a neutral impact on vessel wall characteristics or cardiometabolic biomarkers, an important consideration for safety. However, the generally low CV risk profile of the patients enrolled in this study may have masked potential benefits in these parameters, and also in FMD.

No significant correlations were seen between PASI and FMD, either at baseline or week 12 after secukinumab treatment, which was also the case for patients with severe psoriasis (PASI > 20) at baseline. Although treatment with secukinumab seems to improve both plaque severity and endothelial function, no strong correlation between the strength of the two effects was seen on an individual patient basis. This might be an indicator for a more complex relationship of the two with inhibition of IL-17A. This observation seems to be in agreement with the heterogeneity of CV effects between different psoriasis treatments. In line with this lack of observed correlation, there also appeared to be no association between the level of PASI response attained with secukinumab treatment and the change in FMD from baseline.

Soluble markers indicative of systemic inflammation were elevated at baseline, as expected in those with moderate to severe psoriasis. These and other parameters, including biomarkers of lipid and glucose metabolism, showed no consistent changes with treatment across the study period. All statistical tests and \( p \)-values should be interpreted with caution, because no adjustment for multiple testing was performed. Adiponectin seemed to be reduced consistently in CARIMA, contrary to previous findings of an increase in treated psoriasis patients (Shibata et al., 2011). However, analyses from three pooled phase II studies (n = 667) showed no change in adiponectin over 52 weeks (Novartis data on file). Larger studies of participants with coronary artery disease (CAD) and immune phenotyping are needed to better understand these findings.

There were no deaths and no incident myocardial infarction in this selected low-CV-risk population. No new or unexpected safety signals were observed for secukinumab. Rates of serious infections, *Candida* species infections, and most common adverse events were in line with previous studies of secukinumab.

Although limited by the small sample size and the exploratory nature, CARIMA was designed to systemically investigate the effects of anti-IL-17A on CV markers. The observation of a potential improvement in FMD after long-term secukinumab therapy warrants further testing of the cardiometabolic effects of this effective therapy for plaque psoriasis. There is as yet no established mechanism to link anti-IL-17A directly to the improvement of FMD in patients with psoriasis; any such effect may be mediated directly or indirectly via the influence of IL-17A on reduction of systemic inflammation and oxidative stress that impairs the endothelial vasodilatory capacity. Clearly, these mechanisms require further investigation with careful in vitro and in vivo preclinical studies. At the time of the study design, the label dose of 300 mg secukinumab had not been established; therefore, two different doses were tested, reducing the numbers per group. Given the exploratory nature of the trial, all statistical testing was nominal, and corrections for multiplicity were not applied. Previous studies using FMD as an endpoint have shown wide variation in healthy and psoriatic populations. To address this issue, FMD procedures and training were highly standardized (for details, see Supplementary Materials), and all analyses were performed in a blinded fashion in a core laboratory. However, user-dependent and individual variability cannot be fully excluded, particularly in affecting the interpretation of the week 52 results, for which a placebo control was not available.

Because of the selection of a low-risk population, without established severe CV diseases, most of the secondary parameters were normal at baseline, and no consistent clinically relevant changes were found during the study period. No atherogenic changes were detected. Concomitant use of CV medications, including statins, was permitted during the study, which could further mask potential effects of secukinumab on vascular function. Finally, the proportion of current smokers was high, adding an atherogenic factor and negative effect on vascular endothelial function that may further limit the observation of the effects of secukinumab.

In conclusion, CARIMA showed that FMD was lower in psoriasis patients compared with healthy volunteers and that treatment of plaque psoriasis with anti-IL-17A therapy may result in an improvement of FMD at 52 weeks with no proatherogenic vessel wall changes or alterations in CV biomarkers. This study provides evidence that anti-IL-17A therapy may promote CV health in a population rendered at risk for CAD by psoriasis, but this will need to be confirmed in larger studies with broader CV outcomes and with patients with existing CV comorbidities.

**METHODS**

**Study design and patients**

CARIMA was a multicenter, double-blind, randomized, placebo-controlled, parallel-group, exploratory trial in patients with plaque-type psoriasis (Figure 3). The study was conducted at 23 centers in Germany between April 1, 2014, and April 21, 2016. CARIMA was registered with the German competent authority (Paul-Ehrlich-Institute / PEI) as EudraCT 2013-002266-40 (cf. https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-002266-40/DE).

Patients 18 years of age or older with moderate to severe plaque-type psoriasis (PASI score \( \geq 10 \)) and an inadequate response, intolerance, or contraindication to first-line conventional systemic psoriasis treatments were included. Patients with established severe CV disease including heart failure (ejection fraction < 50% and New York Heart Association class II–IV), valvular heart disease grade II or higher, symptomatic stable or unstable CAD requiring revascularization, history of CAD, uncontrolled hypertension (> 150/90 mm Hg despite therapy), symptoms or findings compatible with the presence of CAD and/or antianginal therapy unless CAD had been ruled out by invasive and/or noninvasive diagnostics, or other inflammatory conditions (except psoriatic arthritis) were excluded. Concomitant medication with vasoactive drugs, including antihypertensive
medication and/or lipid lowering treatments including statins, was permitted if it remained constant throughout the study.

Treatment groups A and B received secukinumab 300 mg (label dose) or 150 mg, respectively, at weeks 0, 1, 2, 3, and 4 and then every 4 weeks until week 48. Treatment groups C and D received placebo until week 12, followed by secukinumab 300 mg or 150 mg, respectively, weekly for 4 weeks then every 4 weeks until week 48. To maintain blinding, patients in groups A and B received weekly placebo injections from weeks 13 to 15, when groups C and D received the initial weekly dose of secukinumab. BSL, baseline; CARIMA, Evaluation of Cardiovascular Risk Markers in Psoriasis Patients Treated with Secukinumab; PBO, placebo; q, every; SEC, secukinumab; Wk, week.

Figure 3. CARIMA study design. CARIMA was a multicenter, double-blind, randomized, placebo-controlled, parallel-group exploratory trial in patients with plaque-type psoriasis. Treatment groups A and B received secukinumab 300 mg (label dose) or 150 mg, respectively, at weeks 0, 1, 2, 3, and 4 and then every 4 weeks until week 48. Treatment groups C and D received placebo until week 12, followed by secukinumab 300 mg or 150 mg, respectively, weekly for 4 weeks then every 4 weeks until week 48. To maintain blinding, patients in groups A and B received weekly placebo injections from weeks 13 to 15, when groups C and D received the initial weekly dose of secukinumab. BSL, baseline; CARIMA, Evaluation of Cardiovascular Risk Markers in Psoriasis Patients Treated with Secukinumab; PBO, placebo; q, every; SEC, secukinumab; Wk, week.

**Study objectives**

The primary objective of the study was the assessment of endothelial function as measured by changes in FMD in patients receiving 300 mg secukinumab compared with placebo. Secondary objectives included changes in FMD at week 52 and changes in arterial stiffness (by PWV and augmentation index), soluble blood biomarkers, and plaque burden by MRI (substudy). PASI scores were also assessed.

**Assessments**

**Endothelial function with FMD.** FMD was assessed at baseline and at weeks 4, 12, 24, and 52 by trained operators according to standard procedures (Ghiadoni et al., 2012; Thijssen et al., 2011) using a high-resolution Doppler ultrasound probe, standardized software, and probe holders (see Supplementary Materials). Vasodilatory drugs, including angiotensin-converting enzyme inhibitors, nitrates, calcium channel inhibitors, and angiotensin receptor blockers, were suspended 12 hours before measurements. FMD values of 49 volunteers (who were not study participants) were acquired twice on the same day to assess reproducibility. No other data were collected from the volunteer population, who were not age or sex matched to participants. The FMD analysis was performed in a blinded fashion by a core laboratory (University Medical Center Mainz; see Supplementary Materials).

**Arterial stiffness.** PWV and augmentation index were measured at baseline and then at weeks 4, 12, 24, and 52. The foot of the arterial pulse wave was recorded using the SphygmoCor XCEL device (AtCor Medical, Itasca, IL) per published methods (see Supplementary Materials) (Hwang et al., 2014).

**Vessel wall MRI.** A substudy was conducted in 33 patients to examine the effects of secukinumab treatment on arterial atherosclerotic plaque burden. This was assessed with MRI to determine carotid and aortic vessel wall area and thickness and normalized wall index (see Supplementary Materials).

**Cardiometabolic biomarkers.** Fasting blood samples were taken for evaluation of soluble biomarkers at baseline and then at weeks 4, 12, 24, and 52. Biomarkers of systemic inflammation, high-sensitivity C-reactive protein (by turbidimetry), and S-100B protein were quantified. Markers of dysglycemia analyzed included fasting plasma glucose, fasting insulin (by chemiluminescence), homeostatic model assessment (β-cell function and insulin resistance), glycated hemoglobin HbA1c, and sex hormone-binding globulin. Also assessed were lipids including triglycerides, total cholesterol, low density lipoprotein cholesterol, high-density lipoprotein cholesterol, apolipoprotein A-1, apolipoprotein B, and adiponectin. Standard laboratory methods were used to evaluate all markers of systemic inflammation and glucose and lipid metabolism (see Supplementary Table S8 online). Other proinflammatory markers were also assessed by Luminex and repeated by ELISA, but they were either below detection limits or were not reproducible between the two assays and therefore are not presented.

**Psoriasis outcome measures.** PASI and investigator’s global assessment (IGA) mod 2011 were used to measure the severity of psoriasis in patients. Skin assessments were conducted at baseline and weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, and 52.

**Safety**

The safety population included all participants who took at least one dose of study treatment during the treatment period. Participants were analyzed according to treatment received. Information on treatment-emergent adverse events and serious adverse events was collected, including severity and potential relationship to study drug.

**Statistical analysis**

The CARIMA study was exploratory in nature, and all statistical tests and P-values are descriptive and should be interpreted with caution. The full analysis set comprised all randomly assigned patients to
whom treatment was administered. All analyses were as observed; missing values were not imputed.

For the primary endpoint, FMD values at week 12 were compared between the secukinumab 300 mg group (label dose, group A) and pooled placebo groups (groups C and D) with an analysis of covariance model with factor treatment and covariate baseline value. The sample size calculation of this exploratory study was based on literature findings in changes in FMD in patients with rheumatoid arthritis after treatment with a biologic at week 12 in comparison to baseline (Kerekes et al., 2011; Tikiz et al., 2010). It was estimated that a sample size of 50 patients in groups A and B and 25 in groups C and D (which were pooled for the analyses up to week 12) would result in a power of 90% (on a 5%, two-sided significance level) if the effect size in percent change in FMD were 2.6 (standard deviation, ± 4).

At week 52, the mean differences in FMD compared with baseline were computed for patients treated with 300 mg secukinumab (label dose) and 150 mg versus baseline. A descriptive P-value and 95% confidence interval were derived using a paired t test.

For other CV markers and soluble biomarkers, the mean differences from baseline within each group were computed, together with a descriptive P-value and a 95% confidence interval (paired t test). The potential correlation of changes in CV markers with changes in PASI score were analyzed by calculation of Pearson correlation coefficients with corresponding P-values.

Changes in FMD were assessed by subgroups in a post hoc analysis of data from week 12 and week 52 in an effort to understand any underlying factors influencing sensitivity to detect a change in FMD. Patients were divided by sex, smoking status (never, former, or current), and Framingham risk score (low risk, < 10%; high risk, ≥10%). For subgroups, an analysis of covariance model with factor treatment and covariate baseline value was used for comparison of least squares mean values adjusted for covariates.

CONFLICT OF INTEREST

EVs received grants from the Deutsche Forschungsgemeinschaft. KR has served as advisor and paid consultant for AbbVie, Amgen, Biogen, Boehringer Ingelheim Pharma, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, Kyowa Kirin, Leo, Lilly, Medac, Merck Sharp & Dohme, Novartis, Ocean Pharma, Pfizer, Regeneron, Sanoﬁ, Takeda, UCB Pharma, and Xenoprot. TR has received research support/principal investigator (clinical trials) from Amgen, Almirall, Astellas, Biogen-Idec, Boehringer-Ingelheim, Celgene, Dignity, Eli Lilly, Forward-Pharma, GlaxoSmithKline, Jansen, Janssen-Cilag, Maruhana, Merck Sharp & Dohme, Mitsubishi Pharma, Novartis, Pfizer, Roche, and Sanofi; has acted as a consultant for Amgen, Biogen-Idec, Celgene, Dignity, Maruhana, Mitsubishi, Novartis, Pfizer, and Xenopor; and has received honoraria from Amgen, Biogen-Idec, Celgene, Jansen, Leo, Pfizer, Roche-Posay, Novartis, and Mundipharma; and has participated in scientific advisory boards for AbbVie, Amgen, Biogen-Idec, Celgene, Eli Lilly, GlaxoSmithKline, Pfizer, Novartis, Jansen, Mundipharma, and Sanofi. WK served on the executive steering committee of JUPITER and CANTOS; served as a consultant for Amgen, DaClor, Kowa, Novartis, Pfizer, and Sanoﬁ; and has received fees for lectures from Amgen, AstraZeneca, Novartis, Pfizer, and Sanoﬁ. AP is a speaker for AbbVie, Almirall-Hermal, Amgen, Biogen-Idec, Celgene, Eli Lilly, Galderma, Jansen, Leo Pharma, Medac, Novartis, Pfizer, and UCB Pharma; served as an advisor for AbbVie, Almirall-Hermal, Amgen, Celgene, Eli Lilly, Jansen, Leo Pharma, Medac, Novartis, and Pfizer; and has participated in clinical trials funded by AbbVie, Almirall-Hermal, Amgen, Biogen-Idec, Boehringer-Ingelheim, Celgene, GlaxoSmithKline, Eli Lilly, Galderma, Hexal, Jansen, Leo Pharma, Medac, Merck Serono, Mitsubishi, Merck Sharp & Dohme, Novartis, Pfizer, Tigrer Cast, Thrombo, and UCB Pharma. AK has received honoraria from Novartis, Eli Lilly, Leo Pharma, Medac, Almirall, Jansen, UCB Pharma, Merck Sharp & Dohme, and Pfizer and has received fees for board participation from Novartis, Leo Pharma, Jansen, and Eli Lilly. TR has received fees and honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, and Novartis. DY, JF, CS, and NM are employees of Novartis.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2018.10.042.

REFERENCES


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