Lowering Interleukin-12 Activity Improves Myocardial and Vascular Function Compared With Tumor Necrosis Factor-α Antagonism or Cyclosporine in Psoriasis

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Background—Interleukin (IL)-12 activity is involved in the pathogenesis of psoriasis and acute coronary syndromes. We investigated the effects of IL-12 inhibition on vascular and left ventricular (LV) function in psoriasis.

Methods and Results—One hundred fifty psoriasis patients were randomized to receive an anti–IL-12/23 (ustekinumab, n=50), anti–tumor necrosis factor-α (TNF-α; etanercept, n=50), or cyclosporine treatment (n=50). At baseline and 4 months post-treatment, we measured (1) LV global longitudinal strain, twisting, and percent difference between peak twisting and untwisting at mitral valve opening (%untwMVO) using speckle-tracking echocardiography, (2) coronary flow reserve, (3) pulse wave velocity and augmentation index, (4) circulating NT-proBNP (N-terminal pro-B-type natriuretic peptide), TNF-α, IL-6, IL-12, IL-17, IL-23, malondialdehyde, and fetuin-a. Compared with baseline, all patients had improved global longitudinal strain (median values: −17.7% versus −19.5%), LV twisting (12.4° versus 14°), %untwMVO (27.8% versus 35%), and coronary flow reserve (2.8 versus 3.1) and reduced circulating NT-proBNP, IL-17, TNF-α, and IL-6 post-treatment (P<0.05). Compared with anti–TNF-α and cyclosporine, anti–IL-12/23 treatment resulted in a greater improvement of global longitudinal strain (25% versus 17% versus 6%), LV twist (27% versus 17% versus 1%), %untwMVO (31% versus 27% versus 17%), and coronary flow reserve (14% versus 11% versus 4%), as well as a greater reduction of IL-12 (−25% versus −4% versus −2%), malondialdehyde (−27% versus +5% versus +26%), and NT-proBNP (−26% versus −13.6% versus +26%) and fetuin-a (P<0.01). Pulse wave velocity and augmentation index were improved only after anti–IL-12/23 treatment and correlated with changes in global longitudinal strain, LV twisting–untwisting (P<0.05).

Conclusions—In psoriasis, IL-12/23 inhibition results in a greater improvement of coronary, arterial, and myocardial function than TNF-α inhibition or cyclosporine treatment.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT02144857. (Circ Cardiovasc Imaging. 2017;10:e006283. DOI: 10.1161/CIRCIMAGING.117.006283.)

Key Words: interleukin-12 • psoriasis • pulse wave analysis • skin disease • ustekinumab

Psoriasis is an immune-mediated skin disease characterized by activation of T helper1 and T helper17 lymphocytes from the excess release of interleukin (IL)-12 and IL-23 from skin dendritic cells. Myocardial dendritic cells also release IL-12 and IL-6, particularly in the failing heart. Activated lymphocytes, as observed in psoriasis, are involved in atherosclerotic plaque rupture. Increased IL-12, IL-6, and tumor necrosis factor (TNF)-α production and oxidative stress characterize psoriatic lesions and are also implicated in myocardial and vascular dysfunction. Thus, psoriasis is a useful clinical model to investigate the effects of anti-inflammatory treatment on myocardial and vascular function. In psoriasis, cyclosporine treatment succeeds disease remission by reducing T-cell activation, though may increase vascular stiffness. Etanercept is a competitive inhibitor of TNF-α by binding to the specific TNF-α cell surface receptors. Ustekinumab is a monoclonal antibody against the common p40 subunit of IL-12 and IL-23 and, thus, inhibits their binding to the IL-12Rβ1 receptor of the T cells. Both biological agents were found effective for the remission of psoriasis.
Because of the major role of IL-12 in atherogenesis and cardiac remodeling and the early release of IL-12 in the inflammatory cascade of psoriasis, we hypothesized that inhibition of IL-12 activity would result in a greater improvement of vascular and myocardial function compared with TNF-α inhibition or cyclosporine treatment.

Thus, in a randomized trial, we compared the effects of a 4-month treatment with anti–IL-12/23 agents (ustekinumab), anti–TNF-α (etanercept) agents, or cyclosporine on left ventricular (LV) myocardial deformation and twisting, coronary microcirculatory function, and arterial elasticity, as well as on cytokines, oxidative stress, NT-proBNP (N-terminal pro-B-type natriuretic peptide), and fetuin-a, a glycoprotein reducing vessel calcium deposition, in psoriatic patients.

Methods

Study Population

We screened patients with plaque-type psoriasis. Exclusion criteria were psoriatic arthritis or inflammatory bowel syndrome, presence of wall motion abnormalities, and ejection fraction.

Table 1. Clinical Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>All (n=150)</th>
<th>Anti–IL-12/23 (n=50)</th>
<th>Anti–TNF-α (n=50)</th>
<th>Cyclosporine (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>50.8±12.4</td>
<td>50.8±14</td>
<td>49±10.5</td>
<td>52.5±11.8</td>
</tr>
<tr>
<td>Sex (male), n (%)</td>
<td>93 (62)</td>
<td>30 (61)</td>
<td>31 (62)</td>
<td>32 (63)</td>
</tr>
<tr>
<td>PASI score</td>
<td>13.3 (7–22)</td>
<td>13.3 (8.7–20.4)</td>
<td>13.8 (6.3–20)</td>
<td>12.8 (6–18)</td>
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<tr>
<td>Risk factors, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>48 (32)</td>
<td>17 (34)</td>
<td>16 (32)</td>
<td>15 (30)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>50 (33)</td>
<td>17 (35)</td>
<td>16 (31)</td>
<td>17 (33)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>68 (45)</td>
<td>24 (47)</td>
<td>23 (45)</td>
<td>21 (43)</td>
</tr>
<tr>
<td>Medication, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>29 (19)</td>
<td>10 (20)</td>
<td>10 (20)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>ACE inhibitors/ARBs</td>
<td>48 (32)</td>
<td>17 (34)</td>
<td>16 (32)</td>
<td>15 (30)</td>
</tr>
<tr>
<td>CCBs</td>
<td>44 (29)</td>
<td>15 (30)</td>
<td>15 (30)</td>
<td>14 (28)</td>
</tr>
<tr>
<td>Statins</td>
<td>45 (29)</td>
<td>15 (30)</td>
<td>15 (30)</td>
<td>15 (30)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>32 (21)</td>
<td>11 (21)</td>
<td>10 (20)</td>
<td>11 (22)</td>
</tr>
</tbody>
</table>

P<0.10 for PASI comparisons among all groups. ACE indicates angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; IL, interleukin; PASI, psoriasis area and severity index; and TNF-α, tumor necrosis factor-a.

Table 2. Markers of Inflammation and Oxidative Stress

<table>
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<tr>
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<th>Anti–IL-12/23 (n=50)</th>
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</table>

P<0.10 for PASI comparisons among all groups. ACE indicates angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; IL, interleukin; PASI, psoriasis area and severity index; and TNF-α, tumor necrosis factor-a.
Figure 1. Interleukin (IL)-12, IL-6, malondialdehyde (MDA), fetuin-a, and NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels, in all patients and in the 3 treatment groups. A, IL-12 decreased only in patients treated with anti–IL-12/23 regimen. B, Greater improvement of IL-6 was observed in patients treated with anti–IL-12/23 and cyclosporine, compared with anti–tumor necrosis factor (TNF)-α regimen. C, MDA decreased in patients treated with anti–IL-12/23, remained unchanged in patients treated with anti–TNF-α regimen, and, conversely, increased in patients treated with cyclosporine. D, Greater improvement of NT-proBNP levels was observed in patients treated with anti–IL-12/23 compared with anti–TNF-α regimen and cyclosporine treatment. E, Fetuin-a levels increased in patients treated with anti–IL-12/23, remained unchanged in patients treated with anti–TNF-α regimen and, conversely, decreased in patients treated with cyclosporine. Solid black dots indicate median values; Bonferroni adjusted $P$ values are quoted.
of ≤50%, history of acute coronary syndrome, familial hyperlipidemia, diabetes mellitus, chronic obstructive pulmonary disease or asthma, moderate or severe valvular heart disease, primary cardiomyopathies, and malignant tumors. Coronary artery disease was excluded in psoriatic patients by absence of clinical history, angina, and reversible myocardial ischemia, as assessed by treadmill test and stress echocardiography. After the exclusion of 16 patients because of inadequate speckle-tracking echocardiography images for analysis (90% feasibility) and 2 more because they missed the 4-month follow-up visit, the final cohort included in the study was 150 patients (psoriasis area and severity index [PASI] disease activity score: median 13.3±12). The disease duration from initial diagnosis until inclusion in the study was 62.2±15 months.
Study Protocol

Patients were randomized to receive an anti–IL-12/23 regimen, namely, ustekinumab 45 mg, SC, at baseline and at 4 and 16 weeks (n=50) after the first injection; an anti–TNF-α regimen, namely, etanercept 50 mg SC, two days per week for 16 weeks (n=50); or cyclosporine 2.5 to 3 mg/kg daily (n=50) for 16 weeks. Randomization was performed by an attending dermatologist (E.P.) using a table of random numbers as reproduced from the online randomization software http://www.graphpad.com/quick-calc/index.cfm. The follow-up period was chosen according to the recommended treatment for ustekinumab.14 In all patients, we performed vascular function studies and LV function assessment on the same day at baseline and 16 weeks after the initiation of treatment. Echocardiography studies followed vascular studies. At baseline and after 4 months of treatment, blood sampling was performed for measurement of markers of inflammation, oxidative stress, and fetuin-a. The PASI was used to monitor the extent of disease and was calculated at baseline and end of treatment to monitor the effect of treatment. The study protocol was approved by the Institute’s Ethics Committee, and written informed consents were obtained from all patients.

Arterial Stiffness and Wave Reflections

Carotid to femoral pulse wave velocity (PWV) was measured using a previously published methodology (Complior; Alam Medical, Vincennes, France).10 PWV was calculated as the distance divided by transit time between waves (m/s). Augmentation index (%) was defined as: 100×peak central systolic blood pressure (cSBP)/central pressure at the inflection point and represents the pressure boost that is induced by the return of the reflected waves at the aorta.

Coronary Flow Reserve

Coronary flow velocity profiles in the left anterior descending artery were obtained using color-guided pulse wave Doppler from long-axis apical projections at rest and after adenosine infusion (140 μg/kg per minute) for 3 minutes according to a previously published methodology.10 In patients with weak Doppler signals, an IV bolus infusion of 0.3 mL of contrast agent (Sonovue, Bracco, Italy) was used to enhance the Doppler signal.10 Coronary flow reserve (CFR) was calculated as the ratio of peak diastolic velocity after adenosine infusion to peak diastolic velocity at rest. Measurements from 3 cardiac cycles were averaged. Inter- and intraobserver variability of these measurements in our laboratory was 5% and 2%, respectively.

Echocardiography

Studies were performed using a Vivid 7 (GE Medical Systems, Horten, Norway) ultrasound system. All studies were digitally stored in a computerized station (Echopac 201; GE Medical Systems, Horten, Norway) and were analyzed by 2 observers, blinded to clinical and laboratory data. All patients had adequate images for analysis. From cross-sectional echocardiographic images, we measured LV end-diastolic volume, end-systolic volume, and ejection fraction (%). Two-Dimensional Strain Measurements

Using a dedicated software package (Echopac), 2-dimensional strain was measured using speckle-tracking analysis. We acquired LV apical 2-, 3-, and 4-chamber views at frame rates ≥50 frames per second. Subsequently, we calculated the global longitudinal strain (GLS) from the apical views (2-, 3-, and 4-chamber) according to previously published methodology.15,16 All variables represent the mean value of measurements taken in 3 consecutive cardiac cycles. Patients with >2 LV segments with poor image quality were rejected from the analysis. The inter- and intraobserver variability of GLS, expressed as relative differences in GLS units, were 7% and 10%, respectively. LV rotation and twisting were assessed using the parasternal LV short-axis views at the basal and the apical level. Therefore, the LV twist curve was automatically generated from the software by calculating the difference between apical and basal rotations at each corresponding time point. Using the pulse wave Doppler recording of mitral valve inflow, we measured the time interval between the onset of the QRS of the
Table 3. Markers of Arterial Stiffness Coronary Microcirculation and Myocardial Deformation

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Anti–IL-12/23</th>
<th>P</th>
<th>Anti–IL-12/23</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>4 mo</td>
<td></td>
<td>Baseline</td>
<td>4 mo</td>
</tr>
<tr>
<td>PWV, m/s</td>
<td>9.4 (7.9 to 12.2)</td>
<td>9.5 (8.2 to 11.4)</td>
<td>0.7</td>
<td>9.3 (7.5 to 13)</td>
<td>8.7 (7.4 to 10.3)</td>
</tr>
<tr>
<td>AI, %</td>
<td>28.2 (13.6 to 35.9)</td>
<td>29.1 (12.5 to 41)</td>
<td>0.6</td>
<td>31 (13 to 42)</td>
<td>27 (7.3 to 40)</td>
</tr>
<tr>
<td>cSBP, mm Hg</td>
<td>127 (113 to 141)</td>
<td>126.5 (115 to 140)</td>
<td>0.6</td>
<td>131 (116 to 155)</td>
<td>123 (115 to 135)</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>75±6</td>
<td>76±8</td>
<td>0.9</td>
<td>76±7</td>
<td>76±9</td>
</tr>
<tr>
<td>LVDD, mm</td>
<td>48.5±4.1</td>
<td>48.3±4</td>
<td>0.8</td>
<td>48.6±4</td>
<td>48.3±3.9</td>
</tr>
<tr>
<td>LVSD, mm</td>
<td>33±2.8</td>
<td>32.7±2.7</td>
<td>0.7</td>
<td>33.1±2.7</td>
<td>32.6±2.6</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>59.9±3.2</td>
<td>60.2±3</td>
<td>0.7</td>
<td>59.8±3.2</td>
<td>60.3±2.9</td>
</tr>
<tr>
<td>GLS, %</td>
<td>−17.7 (−14.6 to 20.6)</td>
<td>−19.5 (−16.3 to 21.4)</td>
<td>0.03</td>
<td>−16.6 (−14 to 20.6)</td>
<td>−20.9 (−17.5 to −22.5)</td>
</tr>
<tr>
<td>LV twisting, °</td>
<td>12.4 (8.6 to 18.9)</td>
<td>14 (9.6 to 18.8)</td>
<td>0.04</td>
<td>11.3 (7.8 to 14.4)</td>
<td>14.4 (9.2 to 17.4)</td>
</tr>
<tr>
<td>Untwist MVO, %</td>
<td>27.8 (21 to 32)</td>
<td>35 (25 to 38)</td>
<td>0.03</td>
<td>32 (22 to 34)</td>
<td>42 (30 to 46)</td>
</tr>
<tr>
<td>CFR</td>
<td>2.8 (2.3 to 3.6)</td>
<td>3.1 (2.45 to 3.6)</td>
<td>0.045</td>
<td>2.8 (1.8 to 3.6)</td>
<td>3.2 (2.5 to 4.3)</td>
</tr>
</tbody>
</table>

(Continued)

Categorical data were compared between patients by contingency tables. Continuous variables were tested for normality using the Kolmogorov–Smirnov test. Normally distributed variables are given as mean±SD. Spearman correlation analysis was used to determine bivariate correlations. Data with a nonsymmetrical distribution are expressed as median (interquartile range) and were analyzed after transformation into ranks.

All analyses were intention to treat. ANOVA (general linear model; SPSS 22; SPSS, Inc, Chicago, IL) for repeated measurements was applied (1) for measurements of the examined markers at baseline, 4 months after treatment used as a within-subject factor and (2) for the effects of treatment (anti–IL-12/23, anti–TNF-α, and cyclosporine), as a between-subject factors. The F and P values of the interaction between time of measurement of the examined markers and type of treatment were calculated. The F and P values of the comparison between treatments were calculated. The Greenhouse-Geisser correction was used when the sphericity assumption, as assessed by Mauchly test, was not met. Post hoc comparisons were performed with Bonferroni correction.

Comparisons between baseline or post-treatment values of measured markers among the 3 treatment groups were performed using factorial ANOVA. Post hoc comparisons were performed with Bonferroni correction. Statistical significance was considered as P<0.05. Baseline variables that were statistically different (P<0.05) among the 3 study groups or were of clinical significance (sex, age, PASI, and atherosclerotic risk factors) were included in multivariate models as covariates.

For post hoc analysis, Bonferroni adjusted P values are quoted. For the determination of interobserver variability, data from the first 20 patients were analyzed by the 2 readers. Intraobserver variability that was assessed by repeat (blind) analysis of the same first 20 examinations was performed a minimum of 4 weeks after the initial assessment with the corresponding technique. Interobserver and intraobserver variabilities were calculated as the SD of the differences between the first and second measurements and expressed as a percentage of the average value.

Results

Clinical characteristics such as age, sex, arterial hypertension, hyperlipidemia, smoking, and medication were similar among the 3 treatment groups (Table 1).

At baseline, all treatment groups had similar values of PASI, biomarkers, and markers of vascular and myocardial function (Tables 2 and 3; P>0.05 for all comparisons). PASI
Table 3. Continued

<table>
<thead>
<tr>
<th>Baseline</th>
<th>4 mo</th>
<th>( p^* )</th>
<th>Baseline</th>
<th>4 mo</th>
<th>( p^* )</th>
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<tbody>
<tr>
<td>9.7 (8.1 to 11.5)</td>
<td>9.5 (8.2 to 11.5)</td>
<td>0.4</td>
<td>9.4 (7.9 to 12.7)</td>
<td>10.9 (8.7 to 13.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>26 (11.1 to 34)</td>
<td>26.4 (16 to 33.3)</td>
<td>0.8</td>
<td>26.2 (13.3 to 33.5)</td>
<td>33.5 (16.9 to 37.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>128 (113.7 to 144.9)</td>
<td>127 (115.2 to 134.6)</td>
<td>0.7</td>
<td>119 (110 to 134)</td>
<td>129 (113 to 139)</td>
<td>0.04</td>
</tr>
<tr>
<td>74±6</td>
<td>76±8</td>
<td>0.8</td>
<td>75±6</td>
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<tr>
<td>48.5±4.1</td>
<td>48.3±4</td>
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<td>48.4±4</td>
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<td>33±2.8</td>
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<td>−17.4 (15.3 to 20.8)</td>
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<td>2.8 (2.2 to 3.4)</td>
<td>3.1 (2.4 to 3.8)</td>
<td>0.04</td>
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Untwist MVO represents percent difference between peak LV twisting and LV untwisting at MVO (%). CAI indicates central augmentation index; CFR, coronary flow reserve; CSBP, central systolic blood pressure; GLS, global longitudinal strain; LV, left ventricular; LVDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVSD, left ventricular end-systolic diameter; MVO, mitral valve opening; and PWV, pulse wave velocity.

*Bonferroni adjusted \( p \) values are quoted.

was similarly improved in all treatment arms at 4-month treatment (Table 2; \( F=1.1; \ p=0.8 \)).

Association of Inflammation and Oxidative Burden With Vascular and Myocardial Function

At baseline, increased PASI was associated with elevated IL-12 \( (r=0.35) \), IL-6 \( (r=0.34) \), and malondialdehyde \( (r=0.30; \ P<0.01) \) for all correlations. Increasing IL-12 and IL-6 levels were related with reduced GLS \( (r=0.40 \text{ and } r=0.38; \ P<0.001) \) and with increased PWV and augmentation index \( (AI; r=0.35 \text{ and } r=0.37; \ P<0.001, \text{ respectively}) \). Increasing IL-17, IL-6, and malondialdehyde were related to reduced CFR \( (r=−0.35, r=−0.31, \text{ and } r=−0.75; \ P<0.001, \text{ respectively}) \). Furthermore, malondialdehyde was related with lower GLS, LV twisting, and percent difference between peak LV twisting and untwisting at MVO \( (r=0.35, r=−0.45, \text{ and } r=−0.47; \ P<0.001, \text{ respectively}) \) in all patients. Finally, increased NT-proBNP was associated with lower GLS and LV twisting \( (r=0.35 \text{ and } r=−0.34; \ P<0.001, \text{ respectively}) \) in all patients.

Association of Vascular Dysfunction With Myocardial Deformation

Reduced LV longitudinal strain and percent difference between peak LV twisting and untwisting at MVO were associated with increased PWV \( (r=0.33 \text{ and } r=−0.40; \ P<0.001) \) and AI \( (r=0.30 \text{ and } r=−0.40; \ P<0.001) \) and decreased CFR \( (r=−0.36 \text{ and } r=−0.40; \ P<0.001) \).

Effects of Treatment on Biomarkers, Vascular Function, and LV Function

Biochemical Markers

Post-treatment, all patients showed decreased values of IL-6 \( (P=0.03) \), IL-17 \( (P=0.03) \), TNF-\( \alpha \) \( (P=0.002) \), and NT-proBNP \( (P=0.02) \) compared with baseline after adjustment for sex, age, PASI, and risk factors (Table 2). In the overall cohort, IL-10 and fetuin-a remained unchanged \( (P>0.10) \), whereas IL-12 showed a borderline reduction \( (P=0.07) \) after treatment (Table 2). However, there was a significant interaction between the type of treatment and changes in biomarkers after treatment \( (P<0.05; \text{ Table 2; Figure 1A through 1E}) \).

Patients on the anti–IL-12/23 treatment had reduced IL-12 and malondialdehyde levels in addition to IL-6, IL-17, and TNF-\( \alpha \), as well as increased fetuin-a levels compared with baseline (Bonferroni adjusted \( P<0.05 \), for all comparisons).

Patients on the anti–TNF-\( \alpha \) regimen had reduced levels of IL-17 and TNF-\( \alpha \) post-treatment (Bonferroni adjusted \( P<0.05 \) for all comparisons) while the levels of the rest biomarkers remained unchanged compared to baseline \( (P>0.10) \).

Patients on cyclosporine treatment had decreased circulating IL-6, IL-17, and TNF-\( \alpha \) (Bonferroni adjusted \( P<0.05 \) for all comparison) but showed increased malondialdehyde \( (P=0.04) \) and reduced fetuin-a \( (P=0.04) \) levels post-treatment compared with baseline.

Compared with TNF-\( \alpha \) inhibition and cyclosporine, inhibition of IL-12/23 activity resulted in a greater reduction in IL-12 \( (−25\% \text{ versus } −4\% \text{ versus } −2\%; \ F=8.1; \ P=0.001; \text{ Figure 1A}) \) and malondialdehyde \( (−27\% \text{ versus } +5\% \text{ versus } +26\% \text{ respectively; } F=7.9; \ P=0.001; \text{ Figure 1C}) \) and NT-proBNP \( (−26\% \text{ versus } −13.6\% \text{ versus } −9.1\%; \ F=8.1; \ P=0.001; \text{ Figure 1D}) \) as well as a greater increase of fetuin-a levels \( (+41\% \text{ versus } +2\% \text{ versus } −47\% \text{, respectively; } F=8.9; \ P<0.001; \text{ Figure 1E}) \). IL-12/23 inhibition also resulted in greater reduction of IL-6 and IL-17 levels than TNF-\( \alpha \) inhibition (Bonferroni adjusted \( P<0.001 \) and \( P=0.03; \text{ Figure 1B} \)) but similar reduction to that achieved by cyclosporine treatment \( (P=0.7 \text{ and } P=0.8; \text{ IL-6: } −17\% \text{ versus } +5\% \text{ versus } −25\% \text{ respectively; } F=7.8; \ P=0.001 \text{ and IL-17: } 56\% \text{ versus } −48\% \text{ versus } −61\%, \text{ respectively; } F=7.9; \ P=0.001) \).

Anti–TNF-\( \alpha \) treatment caused greater reduction of TNF-\( \alpha \) compared with IL-12/23 inhibition (Bonferroni adjusted \( P<0.001 \)).
and cyclosporine ($P<0.01$; $-49\%$ in anti–TNF-$\alpha$ versus $-13\%$ in anti–IL-12/23 versus $-8\%$ in cyclosporine; $F=8.8$; $P<0.001$).

**Vascular Function**

In the overall study cohort, there were no changes in markers of arterial stiffness post-treatment after adjustment for sex, age, PASI, and risk factors (Table 3; $P>0.10$). Coronary flow reserve showed a modest increase in all patients post-treatment ($P=0.045$). However, there was a significant interaction between the type of treatment and changes in vascular markers post-treatment ($P<0.05$; Table 3).

Patients on anti–IL-12/23 treatment had reduced AI (Bonferroni adjusted $P=0.03$), cSBP ($P=0.04$), and PWV ($P=0.04$; Figure 2A) and increased CFR ($P=0.03$; Figure 2B) compared with baseline.

In the anti–TNF-$\alpha$ group, there were no differences of arterial stiffness indices ($P=0.05$) between baseline and post-treatment. Conversely, we observed an increase of CFR post-treatment (Bonferroni adjusted $P=0.04$).

Post cyclosporine treatment, patients showed increased values of AI (Bonferroni adjusted $P=0.03$), cSBP ($P=0.04$), and PWV ($P=0.03$) compared with baseline, whereas there was no change in CFR ($P=0.3$).

Compared with the anti–TNF-$\alpha$ and cyclosporine treatment, the anti–IL-12/23 regimen resulted in greater improvement in PWV ($-10\%$ versus $0.2\%$ versus $16\%$; $F=8.1$; $P=0.001$; Figure 2A), AI ($-13\%$ versus $0.1\%$ versus $19\%$; $F=8.9$; $P=0.001$), and CFR ($14\%$ versus $11\%$ versus $4\%$, respectively; $F=7.9$; $P=0.001$; Figure 2B).

**Myocardial Function**

All patients had improved GLS ($P=0.03$), LV twisting ($P=0.04$), and percent difference between peak LV twisting and untwisting at MVO post-treatment ($P=0.03$), after adjustment for sex, age, PASI, and risk factors (Table 3). However, there was a significant interaction between the type of treatment and changes in LV function markers post-treatment ($P<0.05$; Table 3).

Patients treated with the anti–IL-12/23 or anti–TNF-$\alpha$ regimen had improved GLS, LV twist, and percent difference between peak LV twisting and untwisting at MVO post-treatment compared with baseline (Bonferroni adjusted $P<0.05$; Table 3). Conversely, patients on cyclosporine had no significant changes in GLS ($P=0.1$) and LV twist ($P=0.3$). However, they presented a modest improvement of percent difference between peak LV twisting and untwisting at MVO ($P=0.04$) post-treatment compared with baseline.

Compared with the anti–TNF-$\alpha$ and cyclosporine treatment, the anti–IL-12/23 regimen resulted in greater improvement in GLS (25$\%$ versus 17$\%$ versus 6$\%$, respectively; $F=6.9$; $P=0.01$; Figures 3A and 4), LV twist (27$\%$ versus 17$\%$ versus 1$\%$, respectively; $F=8.0$; $P=0.001$; Figure 3B), and percent difference between peak LV twisting and untwisting at MVO (31$\%$ versus 27$\%$ versus 17$\%$, respectively; $F=7.1$; $P=0.01$).

**Association Between Changes of Biomarkers With Changes in Vascular and Myocardial Function Post-Treatment**

In all patients, the percent increase of GLS correlated with the percent reduction of IL-12 ($r=0.34$), IL-6 ($r=0.37$), malondialdehyde ($r=0.34$), and NT-proBNP ($r=0.40$; $P<0.001$ for all associations) post-treatment. The percent increase of LV twist and increase of the percent difference between peak LV twisting and untwisting at MVO correlated with the respective reduction of malondialdehyde ($r=-0.42$ and $r=-0.44$, respectively; $P<0.001$) and NT-proBNP ($r=-0.36$ and $r=-0.40$; $P<0.001$, respectively). The percent increase of CFR was related with the percent reduction of IL-17 ($r=-0.44$; $P<0.001$).

In patients treated with the IL-12/23 regimen, the percent reduction of PWV and AI correlated with the percent reduction of IL-12 ($r=0.40$; $P=0.003$ and $r=0.02$; $P=0.02$), as well as with the percent increase of fetuin-a levels ($r=0.50$ and $r=0.45$; $P<0.001$). The percent reduction of cSBP was related with the percent reduction of IL-12 ($r=0.41$; $P=0.003$) and IL-6 ($r=0.472$; $P<0.001$).

**Association of Changes of Vascular Markers With Changes of Myocardial Deformation**

In patients treated with IL-12/23 regimen, the percent reduction of PWV and AI and increase of CFR correlated with the percent increase of GLS ($r=0.40$; $P=0.004$; $r=0.41$; $P=0.003$; and $r=0.32$, $P=0.02$), LV twisting ($r=0.44$, $r=0.45$, and $r=0.536$; $P<0.001$), and percent difference between peak LV twisting and untwisting at MVO ($r=0.50$, $r=0.53$, and $r=0.45$; $P<0.001$ for all correlations). The percent reduction of cSBP correlated with the percent increase of GLS ($r=0.410$; $P=0.003$), LV twisting ($r=0.47$, $P<0.001$), and percent difference between peak LV twisting and untwisting at MVO ($r=0.35$; $P=0.01$).

**Discussion**

In this study of patients with psoriasis, treatment with the anti–IL-12/23 agent, ustekinumab, resulted in greater improvement in coronary flow reserve, LV longitudinal myocardial deformation, twisting–untwisting, and NT-proBNP compared with the anti–TNF-$\alpha$ agent, etanercept, and cyclosporine. Treatment with anti–IL-12/23 agent also improved arterial elasticity, whereas anti–TNF-$\alpha$ had a neutral effect and conversely, cyclosporine treatment impaired all markers of arterial elasticity after 4 months of treatment. The improvement of coronary flow reserve and arterial elasticity after IL-12 inhibition was associated with the concomitant improvement of LV myocardial deformation in our study. Finally, we have shown that anti–IL-12/23 treatment caused a greater reduction of IL-12, malondialdehyde, and fetuin-a levels than TNF-$\alpha$ inhibition and cyclosporine treatment. The reduction of IL-12, IL-6, and malondialdehyde levels was associated with improvement myocardial deformation post-treatment in all patients, whereas changes of IL-12 and fetuin-a were related with improved arterial elasticity in the anti–IL-12/23 group.

**Association of Biomarkers With Vascular and Myocardial Function**

IL-12 is the triggering factor of several cytokines in psoriasis (eg, IL-17, IL-6, and TNF-$\alpha$) and has been linked with arterial stiffness in healthy subjects, coronary atherosclerosis, and cardiac remodeling. IL-6 exerts a negative inotropic action and is associated with myocardial ischemia and stunning. In our study, increased...
baseline IL-12 and IL-6 levels were associated with impaired longitudinal myocardial deformation and arterial elasticity in all patients. Elevated IL-17 levels have been associated with endothelial dysfunction, vascular inflammation, and oxidative stress. In our study, increased baseline IL-17 levels were associated with reduced CFR, a marker of coronary microcirculatory damage linked with LV dysfunction.

Oxidative stress, as assessed by malondialdehyde, is found increased in psoriasis and affects vascular and myocardial function. In our study, elevated malondialdehyde was associated with impaired CFR, LV longitudinal deformation, and

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**Figure 2.** Pulse wave velocity (PWV) and coronary flow reserve (CFR) in all patients and in the 3 treatment groups. A, PWV was decreased only in patients treated with anti–interleukin (IL)-12/23, whereas it was increased in patients treated with cyclosporine. There was no significant change of PWV in patients treated with anti–tumor necrosis factor (TNF)-α. B, CFR was improved in all patients post-treatment. Greater improvement was observed in patients treated with anti–IL-12/23 regimen compared with anti–TNF-α and cyclosporine treatment. Solid black dots indicate median values; Bonferroni adjusted P values are quoted.
twisting–untwisting. Thus, IL-12, IL-17, IL-6, and oxidative stress seem to be major determinants of vascular and myocardial function in psoriasis, as also shown for coronary artery disease.

**Effects of Treatment on Vascular Function**

In our study, there was a marked reduction in PWV, AI, and cSBP after IL-12/23 inhibition but not after anti–TNF-α inhibition or
Ikonomidis et al  IL-12 Inhibition and Myocardial and Vascular Function

Furthermore, the percent reduction of IL-12 and increase of fetuin-a levels post anti–IL-12/23 treatment was associated with the percent improvement of markers of arterial elasticity. IL-12 is involved with arterial stiffening, whereas fetuin-a acts as a calcification inhibitor that protects against vascular damage. We may speculate that the neutral effect of anti–TNF-α treatment on arterial stiffness is related to the lack of a significant effect on IL-12 and IL-6 levels, as only these cytokines were related with increased PWV and AI at baseline in our study. Alternatively, the short treatment period

Figure 4. Examples of global longitudinal strain (GLS) changes in each one of the 3 treatment groups. Images show the 4-chamber, 2-chamber, and apical long-axis views with time–strain curves along with bull’s eye plot of the GLS at baseline (Pre) and after (Post) treatment with (A) Anti–interleukin (IL)-12/23 regimen (average GLS post-treatment improved by 26.5% compared with baseline GLS), (B) anti–tumor necrosis factor (TNF)-α regimen (average GLS post-treatment improved by 14% compared with baseline GLS), and (C) cyclosporine (average GLS post-treatment improved by 7.5% compared with baseline GLS).
may have not permitted the detection of changes in arterial stiffness post TNF-α inhibition, as previously shown.23

Central systolic BP was also reduced by IL-12 inhibition in contrast to anti–TNF-α and cyclosporine treatment because the respective reduction of PWV post-treatment caused a delayed arrival of the wave reflection in systole, limiting the systolic augmentation of the aortic pulse wave. This is also confirmed by the respective reduction of the augmentation index only after anti–IL-12/23 treatment.

In our study, there was a greater increase in CFR after IL-12/23 than TNF-α inhibition. Increased IL-17 production causes endothelial dysfunction.22 In our study, elevated baseline IL-17 was associated with reduced CFR, whereas IL-17 reduction post-treatment was associated with the respective increase in CFR. Thus, we may speculate that the greater reduction of IL-17 in addition to IL-12, IL-6, malondialdehyde, and fetuin-a by IL-12 than TNF-α inhibition resulted in the greater effect of anti–IL-12/23 regimen on CFR.

In our study, we observed a detrimental effect of cyclosporine on arterial elasticity and a lack of an effect on CFR after treatment. This adverse effect may be attributed to the reduction of fetuin-a levels, increase in oxidative stress, as assessed by malondialdehyde, and lack of an effect on IL-12 activity, as observed in this study, which counteracted any beneficial effects of the reduced of IL-17 and IL-6, as observed post cyclosporine treatment. Our findings are in agreement with the reported adverse effects of cyclosporine on vascular function.24

Effects of Treatment on Myocardial Function
In our study, psoriatic patients showed a greater improvement in GLS and LV twisting-untwisting after IL-12/23 than TNF-a inhibition or cyclosporine. The improvement in myocardial deformation markers was associated with a respective reduction of NT-proBNP levels. Reduction of IL-12 activity improves LV function and remodeling in heart failure25,26 and acute myocardial infarction.9,20,27 Deficiency of IL-12 is associated with reduced inflammatory cell infiltration, TNF-α and IFN-gamma levels in the heart.20 To this end, we have shown that the anti-IL12/23 and not the anti-TNF-a treatment was effective in reducing circulating IL-12 and IL-6, in line with previous studies for TNF-a inhibition.16 Among the 3 regimens of our study, only the anti-IL12/23 regimen reduced MDA post-treatment. At baseline increased MDA was one of the determinants of impaired LV longitudinal deformation and twisting-untwisting and its reduction after IL-12 inhibition was related with the respective improvement of LV deformation. Thus, we may speculate that treatment with an anti-IL12/23 regimen improves myocardial deformation by its combined effect on oxidative stress and cytokines with adverse cardiovascular action (IL-12, IL-6 and TNFa) compared to the other study regimens. Abnormal arterial elasticity results in dysfunction of the subendocardial myofibrillar fiber helix.16 The function of subendocardial fibers is the major determinant of LV longitudinal myocardial deformation and twisting–untwisting.16 Thus, we may speculate that the greater improvement of arterial elasticity and CFR after IL-12 inhibition may have also contributed to the greater improvement of LV deformation after anti–IL-12/23 treatment compared with the other study regimens.

Study Limitations
The study design does not permit to explore the causality between the changes of the biomarkers with vascular and LV function post-treatment. From the current data, it is not clear whether baseline LV dysfunction is because of coronary microvascular impairment, increased arterial stiffness, negative inotropic effect of inflammatory markers, or oxidative stress that track with disease activity. We cannot exclude that the effects of anti–TNF-α inhibition on vascular and myocardial function may need >4 months of treatment to become evident. Finally, the fact that the study was monocentric and not blinded patients should be acknowledged.

Conclusions
In psoriasis, increased IL-12 activity plays pivotal role in the impairment of arterial elasticity, coronary flow reserve and myocardial deformation. IL-12 inhibition results in a greater improvement of coronary flow reserve, arterial function, and myocardial function than TNF-α inhibition or cyclosporine treatment, suggesting a favorable profile of anti–IL-12/23 regimen on cardiovascular function.

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Disclosures
None.

References


**CLINICAL PERSPECTIVE**

In our study, we have indicated that increased interleukin-12 activity is implicated in the impairment of vascular and myocardial function in patients with psoriasis as it occurs in coronary artery disease. Thus, psoriasis may become an investiga-tional model to assess the effects of anti-inflammatory treatment on cardiovascular function. Anti–interleukin-12/23 treatment resulted in a greater reduction of inflammatory cytokines and improvement of coronary flow reserve, arterial elastic properties, and myocardial deformation, suggesting a more favorable effect on overall cardiovascular function in comparison with treatment with anti–tumor necrosis factor–a regimen and cyclosporine. These findings suggest that inhibition of interleukin-12 activity might be preferable in psoriasis patients who present with several atherosclerotic risk factors and consequently bear an increased atherosclerotic burden and cardiovascular risk. Thus, lowering of interleukin-12 activity may provide a new target to improve vascular and myocardial function in psoriasis and potentially in cardiovascular disease.
Lowering Interleukin-12 Activity Improves Myocardial and Vascular Function Compared With Tumor Necrosis Factor-α Antagonism or Cyclosporine in Psoriasis

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