Psoriasis is a chronic immune-mediated disease affecting up to 3% of the population. Skin and joint inflammation are the hallmarks of psoriasis and an increase in the number of T lymphocytes, antigen-presenting cells, macrophages, and neutrophils is found in psoriatic plaques. The complex interplay between inflammatory cells and keratinocytes induces epidermal proliferation resulting in the typical indurated, scaly, and erythematous plaques of psoriasis. Psoriasis has been shown to increase the risk of myocardial infarction and stroke. Systemic treatments for moderate to severe psoriasis can reduce skin and joint inflammation; however, their effects on vascular inflammation are unknown.

**Methods and Results**—This randomized, controlled trial included 30 patients with moderate to severe psoriasis and a history, or multiple risk factors, of coronary atherosclerosis. Patients were randomized (2:1) to receive either adalimumab subcutaneously for 4 months or to control nonsystemic treatment (topical therapies or phototherapy). Vascular inflammation was measured in the carotid artery and ascending aorta at baseline and week 15, by 18F-fluorodeoxyglucose uptake on positron emission tomography. The change in target:background ratio in the vessel with highest baseline target:background ratio (primary end point) was significant at week 15 compared with baseline for patients randomized to adalimumab (–0.23 [95% CI, −0.39 to −0.08]; \( P=0.004 \)) but not for the control group (–0.10 [95% CI, −0.32 to 0.12]; \( P=0.35 \)). The difference between study arms for this primary end point did not reach statistical significance (–0.13 [95% CI, −0.01 to 0.14]; \( P=0.32 \)). The change in target:background ratio at week 15 improved with adalimumab compared with controls both in the ascending aorta (–0.26±0.11, \( P=0.021 \)) and in carotid arteries (–0.32±0.15, \( P=0.037 \)) when analyzed separately (secondary end points). Changes in other positron emission tomography indices also improved significantly with adalimumab compared with controls in the ascending aorta and carotids. High-sensitivity C-reactive protein decreased by 51% at week 16 with adalimumab compared with 5% in controls (\( P=0.002 \)).

**Conclusions**—The study did not meet its primary end point because the change in target:background ratio in patients randomized to adalimumab was not different from controls. Although adalimumab may reduce vascular inflammation in patients with moderate to severe psoriasis, this effect is not large enough to be demonstrated in a study with a small sample size.

**Clinical Trial Registration**—URL: http://www.clinicaltrials.gov. Unique identifier: NTC00940862. (Circ Cardiovasc Imaging. 2013;6:83-90.)

**Key Words:** aorta ■ atherosclerosis ■ carotid arteries ■ inflammation ■ inhibitors

Psoriasis is a chronic immune-mediated disease affecting up to 3% of the population. Skin and joint inflammation are the hallmarks of psoriasis and an increase in the number of T lymphocytes, antigen presenting cells, macrophages, and neutrophils is found in psoriatic plaques. The complex interplay between inflammatory cells and keratinocytes induces epidermal proliferation resulting in the typical indurated, scaly, and erythematous plaques of psoriasis. Psoriasis has been shown to increase the risk of myocardial infarction and stroke. Psoriasis treatments include topical corticosteroids, vitamin D analogs and phototherapy and also systemic anti-inflammatory agents, such as methotrexate, cyclosporin, or biological agents targeting tumor necrosis factor-\( \alpha \) (TNF-\( \alpha \)) or interleukin (IL)-12/IL-23. These systemic agents all have a profound effect on skin and joint inflammation.

**Clinical Perspective on p 90**

Atherosclerosis is also an inflammatory disease. We hypothesized that treatment-induced reduction in the local inflammatory process in patients with psoriasis would be associated with decreased vascular inflammation as assessed by positron emission tomography/computed tomography (PET/CT).

**Methods**

**Study Design and Patients**

This was an investigator-initiated, single-center, single-blind (cardiologist and all staff involved in vascular imaging and analysis were
PET/CT Image Acquisition
Details of imaging procedures and analyses have been published previously.2 PET/CT imaging was performed at the Montreal Heart Institute after an overnight fast using a GE Healthcare (Milwaukee, WI) Discovery ST PET/CT scanner. Fasting serum glucose levels were checked by fingertip to assure glucose levels <11.1 mmol/L before FDG administration. FDG-PET/CT scans of the carotid arteries and ascending thoracic aorta were performed 10 days before baseline and at week 15. Subjects were injected with 10 mCi of 18F-FDG. Care was taken to ensure that imaging was performed at the same time interval (2 hours) after FDG injection for serial scans, to limit variability in FDG accumulation and background activity. After a 30-second scout, CT scan was acquired (140 kV, 80 mA, 4.25 mm slice thickness) for coregistration and attenuation correction; a 2-dimensional chest PET scan was performed from the aortic arch to the diaphragm. The scan was reconstructed using the OSEM algorithm with corrections applied for normalization, dead time, random events, scatter, attenuation, and sensitivity. A 3-dimensional PET/CT scan of the neck was acquired after stabilizing the neck in a holder to minimize movement and after setting the upper landmark to the superior portion of the auditory meatus in the scout view. This scan was reconstructed using the FORE-IT (iterative reconstruction of Fourier rebinning) with standard parameters.

PET/CT Image Analysis
Image analysis was performed using ITKsnap version 2.2.0 (GNU General public license) and in-house software developed using MATLAB 2010a (Natick, MA). An experienced reader (F.H.) analyzed all scans. All PET/CT measurements were performed at the end of the study, with core laboratory personnel and physician blinded to the randomization assignment. Using the CT images for coregistration, areas of interest were identified on PET scan images of the ascending aorta, right and left carotid arteries. Arterial FDG uptake was quantified by drawing a region of interest around each artery on every slice of the coregistered PET/CT images. The maximal arterial standardized uptake value (SUV) was then calculated as the maximal pixel activity within the region of interest of every slice of the vessel. The mean SUV was also calculated for every slice. The maximum and mean SUVs were measured along the carotid arteries and ascending aorta at ±5 mm intervals, in axial orientation. The SUV is calculated as a time-corrected concentration of tissue radioactivity in kilobecquerels per mL, adjusted for the injected FDG dose and the body weight of the patient, and is a widely used method for quantification of FDG-PET data. The maximal and mean arterial TBR were then calculated by dividing the maximum and mean arterial SUVs by the blood (background) SUV, the latter estimated from the superior vena cavae (for the ascending aorta TBR) and jugular veins (for carotid artery TBR) to produce a blood (background)-corrected artery SUV. This is considered to be a reflection of arterial FDG uptake. For evaluation of the mean FDG blood pool uptake, at least six 3- to 4-mm region of interests were placed in consecutive slices of both jugular veins and superior vena cavae and averaged.

Study Outcomes
The primary end point was the change in the average of maximum TBR values (MeanMAX TBR) of carotid arteries and ascending aorta from baseline to week 15, analyzed in the vessel with highest baseline TBR. Secondary end points included the change in the average of the mean TBR values and the change in the most diseased segment from baseline to week 15 in the vessel with the highest baseline value. Most diseased segment TBR was defined as the 1.5 cm segment that demonstrated the highest PET/CT activity at baseline and was calculated as the MeanMax TBR values derived from 3 contiguous axial segments. The changes in TBR values were also analyzed separately in the carotid arteries and in the ascending aorta.

Changes in hs-CRP and serum lipids (total cholesterol, low-density lipoprotein–cholesterol, high-density lipoprotein–cholesterol, triglycerides), which were all secondary end points, were calculated from baseline to week 16. The proportion of patients reaching 75% improvement in PASI (PASI 75) at week 16 was also evaluated.

Statistical Methods
Because of the exploratory nature of this study, the sample size of 30 patients was not based on formal power calculations. Changes from baseline in PET/CT end points were studied using an ANOVA model adjusting for the baseline value of the end point. Changes from baseline were presented as least square mean estimates and SE. A repeated measures ANCOVA adjusting for baseline was used for the secondary end points of hs-CRP and lipid values. The proportion of patients reaching PASI 75 was compared using a χ² test. For all end points, the analysis was conducted on the intent to treat (ITT) population, and for the last observation carried forward method for missing data were used except for the PASI 75 end point, where a nonresponder imputation method was used. Sensitivity analyses were also performed on the ITT population with complete cases (for the primary end point) and a per-protocol population (for primary and secondary end points). All analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC) with a significance level of 0.05 and prespecified in the statistical analysis plan.

Results
Patient Disposition and Baseline Characteristics
Thirty patients were enrolled in this study and included in the ITT analysis (Figure 1). Baseline characteristics...
Table 1. Baseline Demographics and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Adalimumab</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>56.05±10.95</td>
<td>57.40±7.80</td>
</tr>
<tr>
<td><strong>Men, n</strong></td>
<td>17 (85)</td>
<td>6 (60)</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>95.09±11.53</td>
<td>94.78±17.56</td>
</tr>
<tr>
<td><strong>White, n</strong></td>
<td>20 (100)</td>
<td>10 (100)</td>
</tr>
<tr>
<td><strong>PASI</strong></td>
<td>11.58±5.27</td>
<td>13.13±5.68</td>
</tr>
<tr>
<td><strong>Body surface area with psoriasis</strong></td>
<td>12.15±10.16</td>
<td>13.30±8.10</td>
</tr>
<tr>
<td><strong>Coronary atherosclerosis and risks factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Known coronary atherosclerosis</td>
<td>4 (20)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (65)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>Active smoking</td>
<td>5 (25)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (20)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>14 (70)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>Obesity</td>
<td>19 (95)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Age &gt;55 years</td>
<td>12 (60)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>First degree relative with myocardial infarction &lt;65 years</td>
<td>12 (60)</td>
<td>3 (30)</td>
</tr>
<tr>
<td><strong>Baseline PET/CT values</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeanMAX TBR of vessel with highest baseline TBR</td>
<td>1.96±0.26</td>
<td>2.18±0.44</td>
</tr>
<tr>
<td>MeanMAX TBR of carotid arteries</td>
<td>1.65±0.25</td>
<td>1.84±0.29</td>
</tr>
<tr>
<td>MeanMAX TBR of ascending aorta</td>
<td>1.86±0.35</td>
<td>2.0±0.51</td>
</tr>
<tr>
<td><strong>Baseline lipid values</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.60±0.97</td>
<td>4.68±1.14</td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/L</td>
<td>1.08±0.32</td>
<td>1.05±0.21</td>
</tr>
<tr>
<td>LDL-cholesterol, mmol/L</td>
<td>2.74±0.79</td>
<td>2.84±0.86</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.69±0.80</td>
<td>2.33±1.72</td>
</tr>
<tr>
<td>hs-CRP, mg/L</td>
<td>4.22±3.66</td>
<td>4.28±2.65</td>
</tr>
</tbody>
</table>

*Mean±SD.

HDL indicates high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; MeanMAX, average of maximum values; PASI, psoriasis area severity index; PET/CT, positron emission tomography/computed tomography; and TBR, target:background ratio.

of patients are shown in Table 1. All patients completed the study except 1 who died of a myocardial infarction after week 8. Seven patients were excluded from the per-protocol analysis; 4 started a new medication, and 3 had a dose change in medication that could influence vascular inflammation.

**PET/CT Vascular Results**

For the primary end point of change at week 15 in MeanMAX TBR in the vessel with the highest baseline TBR, the change was significant in the adalimumab group (–0.23±0.07, P=0.004) but not in the control group (–0.10±0.11, P=0.35). The difference of least square means among groups did not reach statistical significance (–0.13±0.13, P=0.32). The same conclusion was reached when the analysis was performed using the Wilcoxon rank-sum test (P=0.695). Sensitivity analyses performed on the per-protocol population and the ITT population with complete cases supported the primary analysis of the ITT population (not shown).

The change (differences of least square means among groups) at week 15 in MeanMAX TBR improved with adalimumab compared with the control group both in the ascending aorta (–0.26±0.11; P=0.021 versus control, Figure 2A) and in carotid arteries (–0.32±0.15; P=0.037 versus control, Figure 2B). The changes in average of the mean TBR values and the change in most diseased segment TBR also improved with adalimumab compared with the control group in the ascending aorta and in carotid arteries, as shown in Table 2 (P=0.010, 0.011, 0.030, and 0.080, respectively). Representative PET/CT images of changes over time in patients of the adalimumab and control groups are shown in Figure 3.

**Psoriasis Evaluation**

The proportion of patients who had at least PASI 75 at week 16 was 70% for patients randomized to adalimumab as compared with 20% for patients in the control group (P=0.01). This difference was also statistically significant when analyzed with Fisher exact test (not shown).

**hs-CRP and Serum Lipids**

hs-CRP levels were significantly decreased in patients randomized to adalimumab compared with those in patients randomized to the control group at days 28, 56, and 112 (P=0.013, 0.008, and 0.002, respectively; Figure 4). The results were supported by those in the per-protocol population (not shown). There were no statistically significant changes over time in serum lipids (Figure 5).
Safety
There were 2 serious adverse events reported; 1 death caused by myocardial infarction, and 1 incidence of lithium toxicity. Both occurred in patients randomized to adalimumab and were deemed to be not related to the study drug by the investigator.

Discussion
This study showed that patients with moderate to severe psoriasis both in the active treatment and control arms had a change in MeanMAX TBR from baseline, and the difference across groups was not significant for the primary end point. However, patients treated for 15 weeks with adalimumab had a statistically significant decrease in vascular inflammation as measured by the change in MeanMAX TBR in the vessel with the highest baseline TBR, whereas the reduction was not significant in the control group (local therapy). The differences between adalimumab and control for MeanMAX TBR, most diseased segment TBR, and average of the mean TBR values were significant both in the carotid arteries and the ascending aorta when evaluated separately (secondary end points). The small sample size of 30, with only 10

Table 2. Changes in TBR on PET/CT Imaging of Ascending Aorta and Carotid Arteries

<table>
<thead>
<tr>
<th>PET/CT End Points</th>
<th>Adalimumab* (n=20)</th>
<th>Control* (n=10)</th>
<th>Differences of LSM*</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary: change in MeanMAX TBR in vessel with highest baseline TBR</td>
<td>$-0.23\pm0.07, P=0.004$</td>
<td>$-0.10\pm0.11, P=0.35$</td>
<td>$-0.13\pm0.13, P=0.32$</td>
<td>$-0.40$ to $0.14$</td>
</tr>
<tr>
<td>Change in MeanMAX TBR of carotid arteries</td>
<td>$-0.08\pm0.08, P=0.33$</td>
<td>$0.24\pm0.12, P=0.050$</td>
<td>$-0.32\pm0.15, P=0.037$</td>
<td>$-0.63$ to $0.02$</td>
</tr>
<tr>
<td>Change in MeanMAX TBR of ascending aorta</td>
<td>$-0.17\pm0.06, P=0.011$</td>
<td>$0.10\pm0.09, P=0.28$</td>
<td>$-0.26\pm0.11, P=0.021$</td>
<td>$-0.48$ to $0.04$</td>
</tr>
<tr>
<td>Change in MDS TBR in vessel with highest baseline TBR</td>
<td>$-0.37\pm0.11, P=0.003$</td>
<td>$-0.21\pm0.16, P=0.18$</td>
<td>$-0.15\pm0.20, P=0.44$</td>
<td>$-0.55$ to $0.25$</td>
</tr>
<tr>
<td>Change in MDS TBR of carotid arteries</td>
<td>$-0.15\pm0.08, P=0.065$</td>
<td>$0.10\pm0.11, P=0.35$</td>
<td>$-0.25\pm0.13, P=0.080$</td>
<td>$-0.52$ to $0.03$</td>
</tr>
<tr>
<td>Change in MDS TBR of ascending aorta</td>
<td>$-0.20\pm0.07, P=0.009$</td>
<td>$0.08\pm0.10, P=0.42$</td>
<td>$-0.29\pm0.12, P=0.030$</td>
<td>$-0.54$ to $0.03$</td>
</tr>
<tr>
<td>Change in meanMEAN TBR in vessel with highest baseline TBR</td>
<td>$-0.18\pm0.06, P=0.004$</td>
<td>$-0.09\pm0.08, P=0.26$</td>
<td>$-0.09\pm0.10, P=0.37$</td>
<td>$-0.28$ to $0.11$</td>
</tr>
<tr>
<td>Change in meanMEAN TBR of carotid arteries</td>
<td>$-0.11\pm0.06, P=0.08$</td>
<td>$0.19\pm0.09, P=0.042$</td>
<td>$-0.30\pm0.11, P=0.011$</td>
<td>$-0.52$ to $0.02$</td>
</tr>
<tr>
<td>Change in meanMEAN TBR of ascending aorta</td>
<td>$-0.08\pm0.04, P=0.067$</td>
<td>$0.12\pm0.06, P=0.049$</td>
<td>$-0.19\pm0.07, P=0.010$</td>
<td>$-0.34$ to $0.05$</td>
</tr>
</tbody>
</table>

*LSM indicates least square means estimates±SEM; meanMAX, average of maximum values; meanMEAN, average of mean values; MDS, most diseased segment; PET/CT, positron emission tomography/computed tomography; and TBR, target:background ratio.
patients in the control group, combined with the choice of vessel with highest TBR as primary end point may be responsible for the fact that the primary end point was not met. Selection of the vessel with the highest baseline inflammation may partially explain the nonsignificant decrease observed in the control group, because higher baseline values usually tend to regress to the mean. Using the observed distribution, the measured change from baseline in TBR and the 2:1 randomization scheme used in the current trial, a sample size of 306 patients would have been required to detect a statistically significant difference for the primary end point. Adalimumab also resulted in a reduction of plasma levels of hs-CRP as early as 4 weeks after initiation of treatment, and the effect lasted until the end of the study at 16 weeks. Finally, patients treated with adalimumab had a substantial improvement in psoriasis. The response rate is almost identical to what has been observed in the pivotal phase III study with adalimumab where 71% of patients achieved PASI 75.10

Atherosclerosis is an inflammatory disease13–19 and patients with different clinical atherosclerotic manifestations are faced with persistent vascular risk despite our current armamentarium. Anti-inflammatory therapies are presently being assessed to reduce further the risk of myocardial infarction and stroke of patients with established vascular disease. Inflammatory diseases, such as psoriasis and rheumatoid arthritis, are now known to expose patients to an increased risk of myocardial infarction and stroke.4–7

Psoriasis is a complex multi-systemic disease influenced by environmental and genetic factors. It is characterized by expansion of Th1, Th17, and Th22 cells resulting in significant inflammation at the skin and joint levels.2

The expression of several cytokines, including TNF-α, interferon-γ, IL-17, IL-22, IL-23, is increased in the skin of patients with psoriasis. Inflammation is a hallmark of psoriasis, and cardiovascular risks have been shown to be higher in patients with more severe cutaneous disease.7 Systemic inflammation is also increased in patients with psoriasis as shown by elevated levels of hs-CRP, but correlation between hs-CRP and myocardial infarction has not been well studied in this patient population. Whether treating patients with moderate to severe psoriasis with an...
FDG-PET imaging has shown a reduction in plaque metabolic activity in large arteries after statin therapy in a small cohort of patients who were not preselected for the presence of vascular disease. More recently, FDG-PET imaging was used to evaluate the effects on vascular inflammation as assessed with 18F-radiolabeled fluorodeoxyglucose (18F-FDG) uptake on PET/CT imaging in a study with a positive response. FDG-PET is a sensitive and reproducible noninvasive technique to measure inflammation based on the accumulation of 18F-FDG in inflamed atherosclerotic plaques. 18F-FDG has been used to image metabolically active macrophages and inflammation. The uptake of 18F-FDG has been shown to correlate with the extent of macrophage infiltration in carotid plaques of patients scheduled for carotid endarterectomy. Carotid inflammation as detected by FDG-PET has been shown to be associated with cardiovascular risk factors. FDG-PET has shown a reduction in plaque metabolic activity in large arteries after statin therapy in a small cohort of patients who were not preselected for the presence of vascular disease. More recently, FDG-PET imaging was also used to evaluate the effects on vascular inflammation of the high-density lipoprotein-raising drug dalcetrapib in patients with atherosclerosis.

In conclusion, the study did not meet its primary end point as the change in TBR in patients randomized to adalimumab was not different from controls. Although adalimumab may reduce vascular inflammation in patients with moderate to severe psoriasis, it did not show a statistically significant decrease in cardiovascular events compared with placebo.

**Figure 5.** Mean serum concentration of high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, total cholesterol, and triglycerides at each visit—adalimumab (A) and control (B). There were no significant changes among groups for lipid values.
severe psoriasis, this effect is not large enough to be demonstrated in a study with a small sample size. The differences between adalimumab and control for secondary PET/CT end points, however, were significant both in the carotid arteries and the ascending aorta. Vascular FDG-PET imaging did not reflect major changes in hs-CRP levels with adalimumab, which may have been because of the small study size or differences between vascular and systemic inflammation in psoriasis.

Acknowledgments

We thank Annik Fortier for her help with statistical analysis and Philippe Marchessault for his assistance in article production.

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Disclosures

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References

Psoriasis is a common inflammatory disease characterized by thick and scaly plaques on the skin. Several studies have shown that psoriasis is an independent risk factor for myocardial infarction and stroke. The reported double-blind controlled study examined the effect of adalimumab, a tumor necrosis factor-α antagonist, on vascular inflammation. Patients were randomized to either adalimumab or a control group. 18F-fludeoxyglucose-positron emission tomography scans were performed before and 16 weeks after treatment to measure vascular inflammation. There was no significant difference between the 2 groups for the primary end point, which was defined as the difference in the change in target:background ratio measured by fludeoxyglucose-positron emission tomography with treatment in the vessel with the highest baseline target:background ratio. However, secondary end points including a significant decrease in target:background ratio in patients randomized to adalimumab, which was not observed in the control group, and the difference between adalimumab and control groups for target:background ratio, when the aorta and carotid arteries were evaluated separately, were statistically significant. Vascular fludeoxyglucose-positron emission tomography imaging also did not reflect major changes in high-sensitivity C-reactive protein levels or clinical improvement in psoriasis with adalimumab, which may have been because of the small study size or because of differences between vascular and systemic inflammation in psoriasis. The clinical significance of reduced vascular inflammation on positron emission tomography/computed tomography imaging and high-sensitivity C-reactive protein levels is uncertain and will need to be determined in larger randomized trials, including studies evaluating the effects of adalimumab on cardiovascular clinical outcomes.

Effects of the Tumor Necrosis Factor-α Antagonist Adalimumab on Arterial Inflammation Assessed by Positron Emission Tomography in Patients With Psoriasis: Results of a Randomized Controlled Trial

Robert Bissonnette, Jean-Claude Tardif, François Harel, Joséphine Pressacco, Chantal Bolduc and Marie-Claude Guertin

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