Effects of the TNF alpha Antagonist Adalimumab on Arterial Inflammation Assessed by Positron Emission Tomography in Patients with Psoriasis: Results of a Randomized Controlled Trial

Bissonnette et al: Adalimumab, Arterial Inflammation and Psoriasis

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Abstract

**Background**—Psoriasis is a chronic inflammatory disease associated with increased risks 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 four months or to control non-systemic treatment (topical therapies or phototherapy). Vascular inflammation was measured in the carotid artery and ascending aorta at baseline and week 15 by $^{18}$F-fluorodeoxyglucose uptake on positron emission tomography (PET). The change in target to background ratio (TBR), in the vessel with highest baseline TBR (primary endpoint) was significant at week 15 as compared to 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 endpoint did not reach statistical significance (-0.13 [95% CI -0.04 to 0.14]; p=0.32). The change in TBR at week 15 improved with adalimumab compared to 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 analysed separately (secondary endpoints). Changes in other PET indices also improved significantly with adalimumab compared to controls in the ascending aorta and carotids. hs-CRP decreased by 51% at week 16 with adalimumab compared to 5% in controls (p=0.002).

**Conclusions**—The study did not meet its primary endpoint 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 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.

**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 erythematosous plaques of psoriasis. Psoriasis has been shown to increase the risk of myocardial infarction and stroke. Psoriasis treatments include topical corticosteroids, vitamin D analogues and phototherapy but also systemic anti-inflammatory agents such as methotrexate, cyclosporin or biological agents targeting tumor necrosis factor alpha (TNF-α) or interleukin-12/interleukin-23. These systemic agents all have a profound effect on skin and/or joint inflammation.

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-centre, single-blind (cardiologist and all staff involved in vascular imaging and analysis were blinded to treatment assignment), randomized, parallel group and active-controlled study (clinicaltrials.gov NTC00940862). Declaration of Helsinki protocols were followed, the study protocol was approved by the Montreal Heart Institute institutional review board, and written informed consent was obtained from each patient. Eligible
patients were 18 to 80 years of age with chronic, moderate to severe plaque type psoriasis covering a minimum of 5% of the body surface area who were candidates for systemic therapy. In addition, patients had to have either a history of coronary atherosclerosis (defined as having at least one narrowing of the diameter of the arterial lumen of ≥50% on coronary angiography, previous myocardial infarction, previous coronary revascularization, abnormal radionuclide myocardial perfusion scan or abnormal stress echocardiogram) or a minimum of three risk factors among the following: hypertension, active smoking, diabetes mellitus, dyslipidemia, obesity, microalbuminuria, age above 55 years, and first-degree relative with evidence of coronary atherosclerosis before 65 years. Patients were also required to show a carotid artery or ascending aorta TBR of ≥1.6 as determined by 18F-FDG uptake measured by PET as evidence of atherosclerotic plaque inflammation. Patients taking medications for angina, hypertension, dyslipidemia or other agents that could have an effect on inflammation must have been on a stable dose for ≥8 weeks before baseline. Patients were excluded if they had a myocardial infarction or hospitalization for a cardiac condition within 12 weeks of baseline, if they had used non-biological systemic therapy for the treatment of psoriasis less than 30 days before Day 0, biological therapy for the treatment of psoriasis less than 90 days before Day 0, phototherapy or topical treatment for psoriasis within the last 2 weeks prior to baseline.

Patients were seen at the dermatology research clinic from May 2009 to June 2011 and were randomized (2:1) to either the TNF-α antagonist adalimumab10 or the control group using a concealed computer-generated code created by the sponsor. Adalimumab was administered subcutaneously with a loading dose of 80 mg followed by 40 mg one week later and every other week thereafter up to and including Week 15. Patients in the control group could use any topical
Psoriasis treatment, ultraviolet B (UVB) phototherapy or no treatment. Psoriasis severity was evaluated at each visit using the PASI.\textsuperscript{11} Fasting serum lipids and hs-CRP were analysed at a local laboratory (CDL laboratories, Montreal, Canada).

\textit{PET/CT image acquisition}

Details of imaging procedures and analyses have been published previously.\textsuperscript{12} PET/CT imaging was performed at the Montreal Heart Institute after an overnight fast using a GE Healthcare (Milwaukee, Wisconsin) Discovery DST PET/CT scanner. Fasting serum glucose levels were checked by fingerstick to assure glucose levels lower than 11.1 mmol/l before FDG administration. FDG-PET/CT scans of the carotid arteries and ascending thoracic aorta were performed approximately ten days before baseline and at Week 15. Subjects were injected with 10mCi of $^{18}$F-FDG. Care was taken to ensure that imaging was performed at the same time interval (two hours) after FDG injection for serial scans, in order to limit variability in FDG accumulation and background activity. After a 30-second scout CT scan was acquired (140kV, 80mA, 4.25 mm slice thickness) for co-registration and attenuation correction, a 2D 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 3D 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 algorithm with standard parameters.
PET/CT image analysis

Image analysis was performed using ITKsnap version 2.2.0 (GNU General public licence) 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 co-registration, 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 (ROI) around each artery on every slice of the co-registered PET/CT images. The maximal arterial standardized uptake value (SUV) was then calculated as the maximal pixel activity within the ROI 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 approximately five 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 three- to four-mm ROIs were placed in consecutive slices of both jugular veins and superior vena cavae and averaged.
Study Outcomes

The primary endpoint was the change in the average of maximum target to background ratio values (MeanMAX TBR) of carotid arteries and ascending aorta from baseline to Week 15, analyzed in the vessel with highest baseline TBR. Secondary endpoints included the change in the average of the mean TBR values (MeanMEAN TBR) and the change in the most diseased segment (MDS TBR) from baseline to Week 15 in the vessel with the highest baseline value. MDS 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 three 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 (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol, triglycerides), which were all secondary endpoints, were calculated from baseline to Week 16. The proportion of patients reaching 75% improvement in psoriasis area and severity index (PASI 75) at Week 16 was also evaluated.

Statistical Methods

Due to 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 endpoints were studied using an analysis of covariance model adjusting for the baseline value of the endpoint. Changes from baseline are presented as least square mean estimates and standard error. A repeated measures analysis of covariance adjusting for baseline was used for the secondary endpoints of hs-CRP and lipid values. The proportion of patients reaching PASI 75 was compared using a chi-square
test. For all endpoints, the analysis was conducted on the ITT population and the last observation carried forward method for missing data was used except for the PASI 75 endpoint where a non-responder imputation method was used. Sensitivity analyses were also performed on the ITT population with complete cases (for the primary endpoint) and a per-protocol (PP) population (for primary and secondary endpoints). All analyses were performed using SAS version 9.2 (Cary, NC) with a significance level of 0.05 and pre-specified in the statistical analysis plan.

Results

Patient disposition and baseline characteristics

Thirty patients were enrolled in this study and included in the intent to treat (ITT) analysis (Figure 1). Baseline characteristics of patients are shown in Table 1. All patients completed the study except one 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 a medication that could influence vascular inflammation.

PET/CT vascular results

For the primary endpoint 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 PP 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 to 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 MeanMEAN TBR and the change in MDS TBR also improved with adalimumab compared to 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 a 75% improvement in psoriasis area and severity index (PASI 75) at Week 16 was 70% for patients randomized to adalimumab as compared to 20% for patients in the control group (p=0.01). This difference was also statistically significant when analyzed with Fisher’s exact test (not shown).

High sensitivity C-reactive protein (hs-CRP) and serum lipids

hs-CRP levels were significantly decreased in patients randomized to adalimumab compared to 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 two serious adverse events reported, one death due to myocardial infarction, and one 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 endpoint. 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, MDS TBR, and MeanMEAN TBR were significant both in the carotid arteries and the ascending aorta when evaluated separately (secondary endpoints). The small sample size of 30, with only 10 patients in the control group, combined with the choice of vessel with highest TBR as primary endpoint may be responsible for the fact that the primary endpoint was not met. Selection of the vessel with the highest baseline inflammation may partially explain the non-significant decrease observed in the control group as 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 randomisation 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 endpoint. 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.5 The expression of several cytokines, including TNF-α, interferon gamma, 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 hsCRP and myocardial infarction has not been well studied in this patient population. Whether treating patients with moderate to severe psoriasis with an anti-inflammatory biological agent could reduce vascular inflammation and future vascular events (myocardial infarctions and strokes) is not known. Some studies based on claims databases or registries have suggested that treatment of rheumatoid arthritis or psoriasis with methotrexate or TNF-α antagonists could decrease the risks of myocardial infarction and/or stroke whereas others have not been able to detect a significant risk difference.20-26 In contrast, a non-statistically significant increase in
major cardiovascular events was observed when patients with psoriasis were treated with antibodies targeting IL-12 and IL-23 compared to placebo.²⁷ Before assessing the value of a TNF-α antagonist such as adalimumab on hard vascular events in a large prospective randomized placebo-controlled study, we first evaluated its effects on vascular inflammation as assessed with ¹⁸F-radiolabeled fluorodeoxyglucose (¹⁸F-FDG) uptake on PET/CT imaging in a study with a positive control arm.

FDG-PET is a sensitive and reproducible non-invasive technique to measure inflammation based on the accumulation of ¹⁸F-FDG in inflamed atherosclerotic plaques.¹⁵, ²⁸-³⁰ 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.³¹ Carotid inflammation as detected by FDG-PET has been shown to be associated with cardiovascular risk factors.³² FDG-PET has shown a reduction in plaque metabolic activity in large arteries following statin therapy in a small cohort of patients that were not preselected for the presence of vascular disease.³³ More recently, FDG-PET imaging was also used to evaluate the effects on vascular inflammation of the HDL-raising drug dalcetrapib in patients with atherosclerosis.¹²

In the current study, patients in the control group could be treated with any topical medication or UVB. There was a numerical decrease in the primary endpoint (MeanMAX TBR in the vessel with the highest baseline TBR) in the control group. Of note, the patient who had the largest and most prominent decrease in TBR (0.87) for the primary endpoint was treated with a super-potent topical corticosteroid and had a 97% decrease in PASI (almost complete skin response). It has
been suggested that inflammation in the skin may increase inflammation in atherosclerotic plaques by the release from skin of activated T cells and cytokines such as IL-1, IL-6 and TNF-α in circulation. This raises the intriguing and testable hypothesis that reduction of cutaneous inflammation using a local treatment such as a very potent topical corticosteroid or UVB may decrease vascular inflammation.

The PET/CT results obtained with adalimumab are concordant with reduced hs-CRP levels as well as the improvement of skin lesions observed in this study group. We however did not observe significant correlations between PET/CT findings and hs-CRP levels or PASI improvement (results not shown). The decrease in hs-CRP level was 51% at end of study for patients randomized to adalimumab as compared to 5% for patients in the control group. Higher hs-CRP levels have previously been shown to be associated with a higher risk of myocardial infarction and stroke. A study where psoriatic patients with an unsatisfactory response to other agents were switched to adalimumab reported a decrease of hs-CRP from 2.1 to 0.3 mg/L but did not include a control group, did not report statistical analysis on hs-CRP data and included patients who had recently been treated with systemic agents for psoriasis.

Vascular FDG-PET imaging used in this study did not reflect major changes in systemic inflammation (hs-CRP) or clinical improvement (PASI) in psoriasis treated with the TNF-alpha antagonist adalimumab. Possible explanations for this discrepancy include the small study size, the relatively short study duration (four months), the lack of prospective power calculation and the potential that vascular inflammation measured by FDG uptake may differ from systemic inflammation in psoriasis. The clinical significance of reduced vascular inflammation on
PET/CT imaging and hs-CRP levels is uncertain and would need to be determined in a large randomized trial evaluating the effects of adalimumab on cardiovascular clinical outcomes.

In conclusion, the study did not meet its primary endpoint 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 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 endpoints 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 due to the small study size or to differences between vascular and systemic inflammation in psoriasis.

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Disclosures

Dr Bissonnette and Dr Bolduc have been investigators, advisors and/or consultants and received
grants and/or honoraria from Abbott, Amgen, Astellas, Novartis, Janssen Ortho, Pfizer, Celgene and Tribute. Drs Tardif, Harel, Pressacco, and Guertin have no conflicts of interest to declare.

References


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, years</strong></td>
<td>56.05 ± 10.95</td>
<td>57.40 ± 7.60</td>
</tr>
<tr>
<td><strong>Male Sex†</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>Caucasian†</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>
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**Coronary atherosclerosis and risks factors†**

<table>
<thead>
<tr>
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<th>Adalimumab</th>
<th>Control</th>
</tr>
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<tbody>
<tr>
<td><strong>Known coronary atherosclerosis</strong></td>
<td>4 (20)</td>
<td>3 (30)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>13 (65)</td>
<td>6 (60)</td>
</tr>
<tr>
<td><strong>Active smoking</strong></td>
<td>5 (25)</td>
<td>4 (40)</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>4 (20)</td>
<td>2 (20)</td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td>14 (70)</td>
<td>6 (60)</td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td>19 (95)</td>
<td>10 (100)</td>
</tr>
<tr>
<td><strong>Age above 55 years</strong></td>
<td>12 (60)</td>
<td>8 (80)</td>
</tr>
<tr>
<td><strong>First degree relative with myocardial infarction before age</strong></td>
<td>12 (60)</td>
<td>3 (30)</td>
</tr>
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</table>

**Baseline PET/CT§ values**

<table>
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<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>**MeanMAX</td>
<td></td>
<td>TBR# of vessel with highest baseline TBR#**</td>
</tr>
<tr>
<td>**MeanMAX</td>
<td></td>
<td>TBR# of carotid arteries**</td>
</tr>
<tr>
<td></td>
<td>Adalimumab n = 20</td>
<td>Control n = 10</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>MeanMAX</td>
<td></td>
<td>TBR# of ascending aorta</td>
</tr>
</tbody>
</table>

**Baseline lipid values* (mmol/L) and hs-CRP** (mg/L)**

<table>
<thead>
<tr>
<th></th>
<th>Adalimumab n = 20</th>
<th>Control n = 10</th>
</tr>
</thead>
<tbody>
<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>

There was no statistically significant difference between the two groups. *mean ± SD, †n (%), ‡PASI: psoriasis area severity index, §PET/CT: positron emission tomography – computed tomography, ||MeanMAX: average of maximum values; #TBR: target-to-background ratio, **hs-CRP: high-sensitivity c-reactive protein, ††HDL: high density lipoprotein, ‡‡LDL: low density lipoprotein.
Table 2. Changes in target-to-background ratio on PET/CT imaging of ascending aorta and carotid arteries.

<table>
<thead>
<tr>
<th>PET/CT* endpoints</th>
<th>Adalimumab† (n=20)</th>
<th>Control† (n=10)</th>
<th>Differences of LSM †</th>
<th>95% Confidence Interval</th>
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<tbody>
<tr>
<td>Primary: Change in MeanMAX‡ TBR§ in vessel with highest baseline TBR§</td>
<td>-0.23 ± 0.07</td>
<td>-0.10 ± 0.11</td>
<td>-0.13 ± 0.13</td>
<td>(-0.40 to 0.14)</td>
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<tr>
<td></td>
<td>p=0.004</td>
<td>p=0.35</td>
<td>p=0.32</td>
<td></td>
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<tr>
<td>Change in MeanMAX‡ TBR§ of carotid arteries</td>
<td>-0.08 ± 0.08</td>
<td>0.24 ± 0.12</td>
<td>-0.32 ± 0.15</td>
<td>(-0.63 to -0.02)</td>
</tr>
<tr>
<td></td>
<td>p=0.33</td>
<td>p=0.050</td>
<td>p=0.037</td>
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<tr>
<td>Change in MeanMAX‡ TBR§ of ascending aorta</td>
<td>-0.17 ± 0.06</td>
<td>0.10 ± 0.09</td>
<td>-0.26 ± 0.11</td>
<td>(-0.48 to -0.04)</td>
</tr>
<tr>
<td></td>
<td>p=0.011</td>
<td>p=0.28</td>
<td>p=0.021</td>
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<tr>
<td>Change in MDS</td>
<td></td>
<td>TBR§ in vessel with highest baseline TBR§</td>
<td>-0.37 ± 0.11</td>
<td>-0.21 ± 0.16</td>
</tr>
<tr>
<td></td>
<td>p=0.003</td>
<td>p=0.18</td>
<td>p=0.44</td>
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<tr>
<td>Change in MDS</td>
<td></td>
<td>TBR§ of carotid arteries</td>
<td>-0.15 ± 0.08</td>
<td>0.10 ± 0.11</td>
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<td>p=0.065</td>
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<tr>
<td>PET/CT* endpoints</td>
<td>Adalimumab† (n=20)</td>
<td>Control† (n=10)</td>
<td>Differences of LSM †</td>
<td>95% Confidence Interval</td>
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<td>-------------------------</td>
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<tr>
<td>Change in MDS</td>
<td></td>
<td>TBR§ of ascending aorta</td>
<td>-0.20 ± 0.07</td>
<td>0.08 ± 0.10</td>
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<tr>
<td>Change in MeanMEAN# TBR§ in vessel with highest baseline TBR§</td>
<td>-0.18 ± 0.06</td>
<td>-0.09 ± 0.08</td>
<td>-0.09 ± 0.10</td>
<td>(-0.28 to 0.11)</td>
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<tr>
<td>Change in MeanMEAN# TBR§ of carotid arteries</td>
<td>-0.11 ± 0.06</td>
<td>0.19 ± 0.09</td>
<td>-0.30 ± 0.11</td>
<td>(-0.52 to -0.08)</td>
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<tr>
<td>Change in MeanMEAN# TBR§ of ascending aorta</td>
<td>-0.08 ± 0.04</td>
<td>0.12 ± 0.06</td>
<td>-0.19 ± 0.07</td>
<td>(-0.34 to 0.05)</td>
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</tbody>
</table>

*PET/CT: positron emission tomography – computed tomography, †LSM: least square means estimates ± SEM: standard error of the mean, ‡MeanMAX: average of maximum values; §TBR: target-to-background ratio, ||MDS: most diseased segment, #MeanMEAN: average of mean values.
Figure Legends

Figure 1. Patient disposition in the study

Figure 2. Change from baseline in MeanMAX TBR in the vessel with the highest baseline TBR (A) and ascending aorta (B) at Week 15. Box-plot representation with median, upper and lower quartile and minimum and maximum value.

Figure 3. Representative examples of changes over time in arterial uptake of FDG on PET/CT images from patients in the control group (A) and adalimumab group (B). Arrows indicate the carotid artery.

Figure 4. High-sensitivity C-reactive protein (hs-CRP) levels at each visit for patients randomized to adalimumab (square) and control (diamond). Geometric means ± SE and p-values between groups are reported at each time point.

Figure 5. Mean serum concentration of HDL-cholesterol, LDL-cholesterol, total cholesterol and triglycerides at each visit – adalimumab (A) and control (B). There were no significant changes among groups for lipid values.
Assessed for eligibility (n=61)

Enrollment

Excluded (n=31)
- Not meeting inclusion criteria (n=28)
- Withdrew consent (n=2)
- Other reasons (n=1)

Randomized (n=30)

Allocated to Control Group (n=10)

Lost to Follow-up (n=0)
Discontinued intervention (n=0)

Allocated to Adalimumab (n=20)

Lost to follow-up (n=0)
Discontinued intervention (n=1)
- AE (death - myocardial infarction) (n=1)

Analysis

Analysed (n=10)

Analysed (n=20)
hs-CRP (mg/l)

Study Days

0  28  56  112

(p=0.013)  (p=0.008)  (p=0.002)
Effects of the TNF alpha 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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