Carotid Intima-Media Thickness in Psoriatic Arthritis

Differences Between Tumor Necrosis Factor-α Blockers and Traditional Disease-Modifying Antirheumatic Drugs

Matteo Nicola Dario Di Minno, Salvatore Iervolino, Rosario Peluso, Raffaele Scarpa, Giovanni Di Minno, on behalf of the CaRRDs study group

Objective—Subjects with psoriatic arthritis (PsA) have an abnormally high prevalence of vascular risk factors (VRFs) and are predisposed to vascular mortality. Tumor necrosis factor (TNF)-α, a major determinant of inflammation, is involved in atherosclerosis. Ultrasonographic carotid intima-media thickness (C-IMT) evaluation allows for subclinical atherosclerosis detection.

Methods and Results—Two hundred twenty-four PsA patients (120 on TNF-α blockers and 104 on traditional disease-modifying antirheumatic drugs [DMARDs]) underwent a C-IMT ultrasound assessment. As many as 305 matched subjects without any inflammatory/rheumatologic disease served as controls. The C-IMT of PsA subjects without VRFs was higher (P<0.0001) than that of controls, the C-IMT of PsA subjects with ≥1 VRF(s) was lower (P<0.0001) than that of controls, and the C-IMT was lower (P<0.0001) in those on TNF-α blockers than in those on DMARDs. Carotid plaques were detected in 15.8% of those on TNF-α blockers and in 40.4% of those on DMARDs (P<0.0001). Treatment duration inversely (β=−0.317, P<0.0001) predicted C-IMT in PsA subjects on TNF-α blockers but not in those on DMARDs (P=0.313).

Conclusion—Among PsA individuals, the C-IMT is higher in subjects on DMARDs than in those on TNF-α blockers. The reduction of inflammation may hamper the cascade that causes the raised vascular risk in PsA patients. (Arterioscler Thromb Vasc Biol. 2011;31:705-712.)

Key Words: atherosclerosis ■ inflammation ■ intima-media thickness ■ psoriatic arthritis ■ tumor necrosis factor-α
and an higher than normal C-IMT have been reported in PsA patients without VRFs. No data on the effect of the combination of the MetS with PsA on the C-IMT are presently available, and no information is available on the effect of different therapeutic strategies on these vascular parameters. In this study, we have performed an ultrasound assessment of the C-IMT in PsA patients and have stratified results according to different treatment schedules (TNF-α blockers or traditional disease-modifying antirheumatic drugs [DMARDs]). In addition, by stratifying according to the presence of major VRFs, we have assessed the interaction of MetS with PsA.

Methods

Subjects

Over a period of 6 months (June 2009 to January 2010), 120 consecutive subjects with PsA, on treatment with TNF-α blockers for at least 1 year (range, 13 to 92 months), who fulfilled the inclusion criteria reported below and who had been attending the Rheumatology Outpatient Clinic of the Federico II University Hospital were evaluated for an ultrasound assessment. As many as 104 PsA patients, chosen among those on traditional DMARD therapy for at least 1 year and comparable to those on TNF-α blockers for sex, age, VRFs, and disease subset, were evaluated in parallel. Thus, as a whole, 224 PsA individuals formed the case group of this study. Adalimumab was used in 52 of them, etanercept in 36, infliximab in 32, sulfasalazine in 28, methotrexate in 62, cyclosporine A in 8, and leflunomide in 6. None was receiving statins or ω-3 fatty acids at the time of the study. All PsA subjects fulfilled the Classification criteria for the diagnosis of Psoriatic Arthritis (CASPAR): (1) evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis; (2) current typical psoriatic nail dystrophy; (3) a negative test result for the rheumatoid factor; (4) current or previous dactylitis; and (5) evidence of juxtaarticular new bone formation, on plain radiographs of the hand or foot. None of the subjects in the case group were on nonsteroidal antiinflammatory drugs or prednisone at the time of the study, nor were any of them receiving combined treatments (TNF-α blockers+DMARDs). All PsA subjects had a clinically active disease (evaluated by the Physician Global Assessment) before being treated with 1 of the 2 treatment schedules. In addition to individual treatment schedules, a trained staff member evaluated disease activity thereof) as needed. Written informed consent was obtained from all the patients. In keeping with recommendations for the use of biological agents in the treatment of PsA,18,19 disease activity was evaluated by using the Bath Ankylosing Spondylitis Disease Activity Index (to evaluate the axial involvement) and the DAS-28 (to evaluate the peripheral involvement). Clinical remission (low-disease activity) was defined by DAS-28 value ≥2.6 or Bath Ankylosing Spondylitis Disease Activity Index value <4.4.

According to National Cholesterol Education Program indications, abdominal obesity was defined as a waist circumference ≥102 cm for men and ≥88 cm for women, hypertriglyceridemia as triglyceride levels ≥150 mg/dL, hypertension as a blood pressure ≥130 mm Hg systolic or ≥85 mm Hg diastolic, and hypercholesterolemia/hypertriglyceridemia as total cholesterol ≥200 mg/dL, with high-density lipoprotein cholesterol as a total cholesterol ≥200 mg/dL, hypercholesterolemia with low-density lipoprotein cholesterol ≥40 mg/dL, for men and ≤50 mg/dL, for women, hypertension as a blood pressure ≥130 or 85 mm Hg, and impaired fasting glucose as a fasting glucose ≥100 mg/dL. Patients were defined as having a MetS if 3 or more of these VRFs were present.

C-IMT Measurements

All ultrasound examinations were performed by the same operator in blinded conditions as to presence/absence of rheumatologic disease and ongoing treatment schedules. After 5 minutes of rest in supine position, the subjects underwent a bilateral carotid ultrasonography with high-frequency, 5-MHz linear-array transducer and a duplex scanner (ESAOTE MyLab 25Gold, Genoa, Italy). The ultrasound examination was performed longitudinally and transversely by using grayscale and color-Doppler ultrasonography imaging. The C-IMT scan protocol requires the visualization of the near and far wall of the right and left common carotid artery (CCA) and carotid bifurcation (bulb) in 3 different projections (anterior, posterior, lateral, and posterior). The CCA intima-media thickness (IMT) was defined as the average of the maximum IMT of the near and of the far wall measurements in the distal CCA (1 cm proximal to the bulb) in each of the 3 projections, and then, the average of the left and the right CCA-IMT was computed (mean-max CCA). The same scan protocol was used to evaluate the bulb (mean-max Bulb), being this also checked for the presence of plaques (ie, of C-IMT ≥1.3 mm). In a reference sample of 400 healthy subjects without VRFs, inflammatory, or rheumatic disease, matched for sex and age with cases and controls of the present study, the mean-max Bulb was 0.57±0.11 mm, the bulb was 0.83±0.19 mm, and the number of subjects with carotid plaques was 27 (6.7%). The reproducibility of the vascular measurement was evaluated in 20 subjects on TNF-α blockers and in 20 on DMARDs within 1 week from the first ultrasonographic examination. The overall r values for the C-IMT was 0.97 (P<0.0001), with a mean difference of 0.008±0.03 (P=0.266). In addition, repeated scans of these 40 subjects were independently analyzed by another ultrasound operator (blinded to rheumatologic disease and ongoing treatments). His overall r value was 0.95 (P=0.001), with a mean difference of 0.01±0.04 (P=0.061) compared with the first reader.

Power and Sample Size

According to the results of a previous study,14 as many as 78 case subjects and 156 control subjects were estimated to be needed to reject the (null) hypothesis that their C-IMT were not statistically different (probability power=90%; Type I error probability associated with the test=5%). On the other hand, based on preliminary results on mean differences (0.1 mm) in C-IMT between PsA subjects on different treatment schedules (TNF-α blockers versus DMARDs), it was estimated that a minimum of 104 subjects for each group of this study. Adalimumab was used in 52 of them, etanercept in 36, infliximab in 32, sulfasalazine in 28, methotrexate in 62, cyclosporine A in 8, and leflunomide in 6. None was receiving statins or ω-3 fatty acids at the time of the study. All PsA subjects fulfilled the Classification criteria for the diagnosis of Psoriatic Arthritis (CASPAR): (1) evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis; (2) current typical psoriatic nail dystrophy, (3) a negative test result for the rheumatoid factor, (4) current or previous dactylitis; and (5) evidence of juxtaarticular new bone formation, on plain radiographs of the hand or foot. None of the subjects in the case group were on nonsteroidal antiinflammatory drugs or prednisone at the time of the study, nor were any of them receiving combined treatments (TNF-α blockers+DMARDs). All PsA subjects had a clinically active disease (evaluated by the Physician Global Assessment) before being treated with 1 of the 2 treatment schedules. In addition to individual treatment schedules, a trained staff member evaluated disease duration and inflammation indices (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], and interleukin 6 [R&D Systems Inc, Minneapolis, Minn]) levels. At the time of the ultrasound assessment, all PsA subjects were also evaluated by the Bath Ankylosing Spondylitis Disease Activity Index, the Disease Activity Score-28 (DAS-28), and the Visual Analogical Scale (for pain evaluation). The staff also collected data as to demographic parameters and VRFs of cases and controls. The control group consisted of 305 subjects without any inflammatory or rheumatologic disease, matched with PsA subjects for sex, age, and VRFs. It was chosen among individuals referred to our thrombosis unit over the same time period to undergo a carotid ultrasound assessment for cardiovascular prevention. All had been receiving, for at least 6 months, a high-fiber diet and statins, antihypertensive, or oral hypoglycemic drugs (or a combination thereof) as needed. Written informed consent was obtained from each subject. In addition to the lack of informed consent, exclusion criteria were as follows: age <18 years, high-grade stenosis or a history of carotid endarterectomy/stenting, familial hypercholesterolemia/hypertriglyceridemia, III or IV New York Heart Association (NYHA) class congestive heart failure, cardiac arrhythmia, angina/ recent vascular events, or a history of venous thrombosis.
case group was needed (probability power=80%; type I error probability associated with the test=5%).

**Statistical Analysis**

Statistical analysis was performed with the SPSS 16 system (SPSS Inc., Chicago, IL). Because C-IMT is not normally distributed, all the analyses were performed after log transformation. Continuous data were expressed as means±SD, and categorical variables were expressed as percentages. To compare continuous variables, an independent sample *t* test was performed, and correlation was assessed using the Pearson linear correlation coefficient (r). In addition to being evaluated as continuous variables, abdominal obesity, triglyceride levels, total cholesterol, high-density lipoprotein cholesterol, blood pressure, and fasting glucose were also analyzed in dichotomous (1/0) categories. Smoking status and MetS were defined by 2 dichotomous (yes/no) categories as well. To analyze categorical data, the *χ*² test was performed. When the minimum expected value was < 5, the Fisher exact test was used. The ANOVA with the Bonferroni post hoc test was used to evaluate differences in C-IMT as related to the use of different drugs. To make predictions, a linear regression (stepwise) model was adopted, with C-IMT as the dependent variable and ESR, CRP, sex, age, type of treatment (TNF-α blockers versus DMARDs), treatment and disease duration, disease activity, smoking habit, diabetes, obesity, hypercholesterolemia, hypertriglyceridemia, and hypertension as independent variables. All the results are presented as 2-tailed values with statistical significance if probability values were <0.05.

**Propensity Score Analysis**

An attempt was made to check whether PsA subjects were matched, based on the probability (propensity) of receiving TNF-α blockers versus DMARDs. The predicted probability of receiving 1 of the 2 treatments was estimated for each patient by using a multivariate logistic regression model in which the treatment schedule was the dependent variable and baseline patient characteristics (age, sex, diabetes mellitus, hypertension, hypercholesterolemia, hypertriglyceridemia, obesity, smoking habit) were the independent variables. Consistent with the notion that no established predictor helps identify individuals who will need TNF-α blockers, the 2 treatment groups appeared to be entirely matched for baseline characteristics. Thus, no propensity matching was needed for further analysis.

### Table 1. Demographic and Clinical Features of the Study Population and Stratification According to Treatment Schedules

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study Population</th>
<th>Treatment Schedules</th>
</tr>
</thead>
</table>
|                                  | PeA Subjects,  
|                                  | n=224            | Controls,  
|                                  |                  | n=305               |  
|                                  |                  |                     |  
|                                  |                  | PsA Subjects on  
|                                  |                  | TNF-α Blockers,  
|                                  |                  | n=120               |  
|                                  |                  | PsA Subjects on  
|                                  |                  | DMARDs,  
|                                  |                  | n=104               |  
|                                  |                  |                     |  
| Age                              | 52.61±11.37      | 51.88±12.40         | 0.488               |  
| Male sex                         | 104 (46.4)       | 132 (43.3)          | 0.480               |  
| MetS                             | 76 (33.9)        | 89 (29.2)           | 0.255               |  
| Impaired fasting glucose         | 20 (8.9)         | 28 (9.2)            | 1.000               |  
| Hypertension                     | 92 (41.1)        | 108 (35.4)          | 0.204               |  
| Hypercholesterolemia with low    | 116 (51.8)       | 168 (55.1)          | 0.481               |  
| high-density lipoprotein         |                  |                     |                     |  
| Hypertriglyceridemia             | 60 (26.8)        | 78 (25.6)           | 0.765               |  
| Obesity                          | 140 (62.5)       | 197 (64.6)          | 0.648               |  
| Smoking habit                    | 64 (28.6)        | 102 (33.4)          | 0.256               |  
| Disease duration (months)        | 109.04±71.9      | ...                 | ...                 |  
| Pattern of PsA                   |                  | 113.62±58.24        | 103.79±85.91        | 0.312               |  
| Distal joint disease             | 0 (0)            | ...                 | ...                 |  
| Oligoarthritis                   | 52 (23.2)        | ...                 | ...                 |  
| Spondylarthropathy               | 76 (33.9)        | ...                 | ...                 |  
| Polyarthritis                    | 84 (37.5)        | ...                 | ...                 |  
| Mutilans                         | 12 (5.4)         | ...                 | ...                 |  
| Disease activity (baseline) PGA  | 64.91±12.6       | ...                 | ...                 |  
| Treatment characteristics        |                  | 74.67±11.5          | 53.65±13.9          | <0.0001             |  
| Treatment duration (months)      | 55.10±26.7       | ...                 | ...                 |  
| Disease activity (post-treatment)|                  | 52.33±24.11         | 58.22±29.21         | 0.100               |  
| Low disease activity             | 118 (52.7)       | ...                 | ...                 |  
| ESR (mm)                         | 18.81±12.3       | ...                 | ...                 |  
| CRP mg/dl                        | 2.73±2.75        | ...                 | ...                 |  
| Interleukin 6 (ng/L)             | 4.41±0.69        | ...                 | ...                 |  
| Post-treatment ultrasound evaluation |                  | ...                 | ...                 |  
| mean-maxCCA (mm)                 | 0.75±0.22        | 0.80±0.24           | 0.005               |  
| mean-maxBulb (mm)                | 1.08±0.45        | 1.29±0.41           | <0.001              |  
| Carotid plaques, n (%)           | 61 (27.2)        | 186 (61.0)          | <0.001              |  

PGA indicates physician globe assessment.
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(mean-maxCCA and mean-maxBulb) significantly higher than those
shown in Table 2, PsA subjects without VRF had a C-IMT
higher than those of control subjects. In subjects with 1 to 3 risk factors, the
C-IMT of PsA subjects was significantly lower than that of
control subjects. In subjects with 1 to 3 risk factors, the
C-IMT of PsA subjects was significantly lower than that of
case and control subjects.

Table 1 reports demographic and clinical characteristics of
PsA, n=224 Controls, n=305 P
PsA, n=224 Controls, n=305 P
0 VRF 0.72±0.25 0.56±0.08 0.025 1.09±0.40 0.87±0.21 0.032
n 20 24 0.18 0.218
1 VRF 0.69±0.24 0.78±0.14 0.001 0.96±0.44 1.24±0.34 <0.0001
n 60 67 0.25 0.004
2 VRF 0.70±0.17 0.78±0.19 0.006 1.02±0.50 1.29±0.41 <0.0001
n 52 90 0.21 0.001
3 VRF 0.75±0.15 0.86±0.31 0.040 1.09±0.35 1.37±0.45 <0.0001
n 44 74 0.25 0.10
4 VRF 0.88±0.25 0.88±0.31 0.833 1.25±0.43 1.39±0.43 0.126
n 44 39 0.25 0.10
5 VRF 0.91±0.13 0.96±0.19 0.720 1.37±0.65 1.42±0.37 0.633
n 4 11 0.25 0.10

All P values are for log-transformed values of CCA and bulb. n indicates number of subjects.

Results

Table 1 reports demographic and clinical characteristics of
case and control subjects.

Among cases, PsA subjects on TNF-α blockers and those on
traditional DMARDs significantly differed as to C-IMT measurements (Table 1). Accordingly, carotid plaques were found in 15.8% (n=19) of subjects on TNF-α blockers and in 40.4%
(n=42) of subjects on traditional DMARDs (P<0.0001). As shown in Table 2, PsA subjects without VRF had a C-IMT (mean-maxCCA and mean-maxBulb) significantly higher than those of control subjects. In subjects with 1 to 3 risk factors, the
C-IMT of PsA subjects was significantly lower than that of
controls, whereas in subjects with ≥3 VRFs, no significant
difference was present between PsA and control subjects.

Baseline Physician Global Assessment significantly dif-
fered between PsA subjects on TNF-α blockers and those on
traditional DMARDs (Table 1). Because TNF-α blockers
should be used only after the failure of traditional DMARDs,
the worse control of disease activity before starting treatment with TNF-α blockers is in keeping with current recommendations for the use of biological agents in PsA.18,19 Clinical remission was present in 73.3% (88 of 120) of subjects on TNF-α blockers and in 28.8% (30/104) of subjects on
traditional DMARDs (odds ratio, 0.147; 95%CI: 0.064 to
0.338; P=0.001). Inflammation reactants (ESR, CRP) were
significantly lower in subjects on TNF-α blockers than in those on DMARDs (ESR:14.23±8.53 versus 24.11±16.66,
P<0.0001; CRP:1.98±1.8 versus 3.6±3.9, P=0.007). Inter-
leukin 6 levels did not differ (P=0.07). The C-IMT of PsA
subjects stratified according to treatment schedule and to
MetS is presented in Table 3. Although it is relevant in
subjects on DMARDs, the MetS was not associated with
differences in C-IMT in subjects on TNF-α blockers.

Table 2. IMT (CCA and Bulb) in Subjects With PsA According to the Number of VRFs

<table>
<thead>
<tr>
<th>No. of Risk Factors</th>
<th>PsA, n=224</th>
<th>Controls, n=305</th>
<th>P</th>
<th>PsA, n=224</th>
<th>Controls, n=305</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 VRF</td>
<td>0.72±0.25</td>
<td>0.56±0.08</td>
<td>0.025</td>
<td>1.09±0.40</td>
<td>0.87±0.21</td>
<td>0.032</td>
</tr>
<tr>
<td>n</td>
<td>20</td>
<td>24</td>
<td></td>
<td>20</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>1 VRF</td>
<td>0.69±0.24</td>
<td>0.78±0.14</td>
<td>0.001</td>
<td>0.96±0.44</td>
<td>1.24±0.34</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>n</td>
<td>60</td>
<td>67</td>
<td></td>
<td>60</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>2 VRF</td>
<td>0.70±0.17</td>
<td>0.78±0.19</td>
<td>0.006</td>
<td>1.02±0.50</td>
<td>1.29±0.41</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>n</td>
<td>52</td>
<td>90</td>
<td></td>
<td>52</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>3 VRF</td>
<td>0.75±0.15</td>
<td>0.86±0.31</td>
<td>0.040</td>
<td>1.09±0.35</td>
<td>1.37±0.45</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>n</td>
<td>44</td>
<td>74</td>
<td></td>
<td>44</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>4 VRF</td>
<td>0.88±0.25</td>
<td>0.88±0.31</td>
<td>0.833</td>
<td>1.25±0.43</td>
<td>1.39±0.43</td>
<td>0.126</td>
</tr>
<tr>
<td>n</td>
<td>44</td>
<td>39</td>
<td></td>
<td>44</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>5 VRF</td>
<td>0.91±0.13</td>
<td>0.96±0.19</td>
<td>0.720</td>
<td>1.37±0.65</td>
<td>1.42±0.37</td>
<td>0.633</td>
</tr>
<tr>
<td>n</td>
<td>4</td>
<td>11</td>
<td></td>
<td>4</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. C-IMT (CCA and Bulb) in PsA Subjects Stratified According to Treatment Schedule and to Presence of MetS

<table>
<thead>
<tr>
<th>PsA Individuals: Whole Sample (n=224)</th>
<th>MetS, No (n=148)</th>
<th>MetS, Yes (n=76)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean-maxCCA (mm)</td>
<td>0.72±0.21</td>
<td>0.81±0.23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>mean-maxBulb (mm)</td>
<td>1.01±0.44</td>
<td>1.21±0.44</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

PsA Individuals on Traditional DMARDs
(n=104)

<table>
<thead>
<tr>
<th>MetS, No (n=64)</th>
<th>MetS, Yes (n=40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean-maxCCA (mm)</td>
<td>0.75±0.25</td>
<td>0.89±0.24</td>
</tr>
<tr>
<td>mean-maxBulb (mm)</td>
<td>1.11±0.53</td>
<td>1.43±0.46</td>
</tr>
</tbody>
</table>

PsA Individuals on TNF-α Blockers
(n=120)

<table>
<thead>
<tr>
<th>MetS, No (n=84)</th>
<th>MetS, Yes (n=36)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean-maxCCA (mm)</td>
<td>0.69±0.18</td>
<td>0.72±0.19</td>
</tr>
<tr>
<td>mean-maxBulb (mm)</td>
<td>0.93±0.33</td>
<td>0.98±0.25</td>
</tr>
</tbody>
</table>

All P values are for log-transformed values of CCA and bulb.
Correlation studies are reported in Figure 1. In those on traditional DMARDs, the mean-max Bulb showed a direct correlation with treatment ($r = 0.321$, $P = 0.001$) and with disease ($r = 0.392$, $P < 0.001$) duration. In the same group, mean-max CCA showed a direct correlation with disease duration ($r = 0.203$, $P = 0.039$). In keeping with this, the presence of carotid plaques showed a significant direct correlation with treatment duration ($r = 0.270$, $P = 0.006$) and with disease duration ($r = 0.320$, $P = 0.001$). Accordingly, subjects with ultrasound evidence of carotid plaques had a disease duration significantly longer than that of subjects without (130.34 ± 106.75 versus 101.09 ± 52.56, $P = 0.007$). No correlation with treatment duration was documented in PsA subjects on DMARDs when the mean-max CCA was examined. In those on TNF-α blockers, whereas no significant correlation was found between disease duration and C-IMT (mean-max CCA: $r = -0.005$, $P = 0.954$; mean-max Bulb: $r = 0.011$, $P = 0.904$), a significant inverse correlation between treatment duration and C-IMT was found (mean-max CCA: $r = -0.319$, $P < 0.001$; mean-max Bulb: $r = -0.296$, $P = 0.001$). The presence of carotid plaques inversely correlated with treatment duration ($r = -0.206$, $P = 0.024$) and did not show a significant correlation ($r = 0.014$, $P = 0.877$) with disease duration.

In a linear regression model, age ($\beta = 0.382$, $P < 0.0001$), male sex ($\beta = 0.134$, $P = 0.009$), treatment with traditional DMARDs ($\beta = 0.202$, $P = 0.001$), and clinical remission ($\beta = -0.236$, $P < 0.0001$) independently predicted the C-IMT (whole PsA sample). Among VRFs, hypertension ($\beta = 0.221$, $P < 0.0001$) independently predicted the C-IMT in this setting, as did the number of VRFs ($\beta = 0.225$, $P < 0.0001$).

When the patient population was stratified according to treatment schedules, whereas age predicted C-IMT both in the DMARDs group ($\beta = 0.371$, $P < 0.0001$) and in the TNF-α blocker group ($\beta = 0.302$, $P < 0.0001$), ESR levels directly predicted CCA thickness ($\beta = 0.254$, $P = 0.001$) in PsA subjects on DMARDs but not in those on TNF-α blockers. In keeping with this, arterial hypertension predicted the C-IMT only in subjects on DMARDs treatment ($\beta = 0.646$, $P < 0.0001$). On the other hand, treatment duration significantly and independently ($\beta = -0.317$, $P < 0.0001$) predicted the C-IMT in those on TNF-α blockers but not in those on traditional DMARDs. An effort was also made to evaluate C-IMT in PsA patients as related to drugs used. In spite of the small sample size, the lowest C-IMT was found in subjects on treatment with drugs achieving the strongest antiinflammatory effect (Figure 2).
Discussion

The atherosclerotic process starts in childhood. The identification of preclinical atherosclerosis before vascular events is needed to allow for appropriate prevention. Noninvasive surrogate markers have been developed to allow for an early detection of atherosclerosis. High-resolution ultrasonographic measurement of the C-IMT is 1 such method. C-IMT can be used as a predictor of future vascular events in otherwise healthy individuals. PsA patients experience premature vascular mortality. However, with 1 exception, little is known regarding their C-IMT. The present report confirms that in the absence of VRFs, the C-IMT of PsA individuals is significantly higher than that of controls. However, when stratified according to the presence of VRFs, the C-IMT of PsA individuals is lower than that of controls (Table 2). The finding that in the presence of 1 to 3 VRFs, PsA subjects have a lower C-IMT as compared with controls may be taken to suggest a protective effect of antiinflammatory drugs on the C-IMT. On the other hand, because an higher C-IMT is predicted by an increasing number of VRFs in PsA subjects, an additive effect of VRFs can be postulated to overcome the protective effect of antiinflammatory drugs. However, the C-IMT was lower in PsA subjects on TNF-α blockers than in those on traditional DMARDs (Tables 1 and 3) and the coexistence of a MetS was associated with higher C-IMT in subjects on DMARDs than in those on TNF-α blockers (Table 3).

Over the past decade, TNF-α blockers have provided a significant advancement for preventing the progression of inflammation and of the structural damage of joints in patients with psoriasis, PsA, or rheumatoid arthritis. In addition, TNF-α blockers improve the endothelial function and the vascular risk profile in patients with immune-mediated disorders. In the present study, the effects elicited by TNF-α blockers appear to be accounted for by subtle antiinflammatory mechanisms. ESR levels significantly predicted mean-max CCA thickness only in PsA subjects on DMARDs. ESR and CRP were significantly lower in subjects on TNF-α blockers than in those on DMARDs.

By inhibiting proinflammatory cytokines involved in insulin regulation, lipid metabolism and in body weight homeostasis, TNF-α blockers reduce the prevalence of the MetS in subjects with rheumatologic disease. Consistent with a large body of evidence, as much as 35% to 40% of the present PsA sample exhibited the MetS (Table 1). However, at variance with subjects on DMARDs, the MetS was not associated with differences in C-IMT in subjects on TNF-α blockers (Table 3). Accordingly, clinical remission was present in 73.3% of subjects on TNF-α blockers and in 28.8% of those on traditional DMARDs.

Consistent with the concept that the reduction of systemic inflammation may hamper the cascade that leads to enhanced vascular risk in PsA patients, the present study documents a significantly reduced C-IMT in patients on TNF-α blockers as compared with those on DMARDs.

In addition, our data show that although it is largely independent of disease duration and preexisting atherogenic risk factors featuring the MetS, the efficacy of TNF-α blockers was related to treatment duration. This is consistent with a progressive effect of inflammation on the C-IMT. Our study has several potential limitations. The choice of the comparator group reflects the apparent heterogeneity of the population that is referred to a second-level outpatient clinic. Usually, controls are not evaluated with the same rigor as the cases. However, our controls were chosen among subjects who had been referred to the vascular unit of our clinic to undergo a carotid ultrasound assessment for vascular prevention. When a disease is relatively rare (as is the case for PsA), studies often have a small sample size. This increases variability, often leading to nonsignificant comparisons. However, sampling bias could become a confounder if the reason for the heterogeneity influences the decision on how to report the results (eg, mean or maximal C-IMT). As in most previous comparisons in immune-mediated disorders, we report a mean-max C-IMT in the present setting.

Because TNF-α blockers should be used in PsA individuals only after the failure of traditional DMARDs, a randomized study in this pathological setting is almost unfeasible. To...
adjust for selection bias when assessing causal effects, the propensity score analysis33,24 was used: the 2 treatment groups were found to be entirely matched for baseline characteristics, so that no propensity-matching was needed for further analysis. The latter lends credence to the possibility that the present data provide insight into cardiovascular complications occurring in PsA subjects.

Limitations in the reproducibility of the ultrasound determinations should also be considered. However, the precision of the measurements, as exemplified by the very high reproducibility in PsA subjects reevaluated within 1 week from the first ultrasonographic examination, makes it unlikely that we were unable to detect truly significant changes in arterial-wall thickness using our measurement technique.

Growing serum cholesterol plasma levels is a common side effect of treatments with certain antirheumatic drugs. A recently developed dyslipidemia was the reason why they were referred to our unit to refine their cardiovascular risk. Although more than 50% of PsA subjects in the present setting had a hypercholesterolemia, none of them was on statins. In the Atherosclerosis Progression in Familial Hypercholesterolemia study,33 the progression in IMT was significantly reduced by the administration of statins. Adequate treatment for their vascular risk was given to each of PsA subjects following the present evaluation. Currently, the majority of patients with the combination of VRFs, such as those with the MetS, are treated with high-dose statins. Accordingly, control subjects were already under statin treatment.

Because the sample size was calculated to compare TNF-α blockers with DMARDs, the stratification according to different drugs (Figure 2) should be taken with caution. However, it implies that appropriately designed studies, aimed at evaluating differences in the C-IMT according to different antirheumatic drugs should be carried out. Although validity, feasibility, and accuracy of C-IMT need to be further strengthened, the present data provide a rationale for using such measurement to prospectively evaluate newer strategies that decrease the risk of vascular events in PsA and to identify subgroups of PsA subjects that maximally benefit from such strategies.

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Disclosures

During the last 5 years, Prof Giovanni Di Minno and Professor Raffaele Scarpa served on advisory boards and received honoraria and grants for research unrelated to this study, but they did not receive specific funding for the preparation of this article. The other authors have nothing to declare.

References


Carotid Intima-Media Thickness in Psoriatic Arthritis: Differences Between Tumor Necrosis Factor- \( \alpha \) Blockers and Traditional Disease-Modifying Antirheumatic Drugs
Matteo Nicola Dario Di Minno, Salvatore Iervolino, Rosario Peluso, Raffaele Scarpa and Giovanni Di Minno

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