Hemostatic and Fibrinolytic Changes Are Related to Inflammatory Conditions in Patients with Psoriatic Arthritis — Effect of Different Treatments

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ABSTRACT. ***Objective.*** To prospectively evaluate the effect of tumor necrosis factor (TNF)-α inhibitors on hemostatic and fibrinolytic variables in subjects with psoriatic arthritis (PsA).

Methods. Among subjects with PsA who were taking traditional disease-modifying antirheumatic drugs (DMARD), 98 patients with active disease who switched to treatment with TNF-α inhibitors were enrolled in this study (Group 1). In parallel, 98 matched subjects with minimal disease activity (MDA) and treated with DMARD were enrolled (Group 2). In all patients, hemostatic and fibrinolytic variables were evaluated at enrollment and after a 6-month followup. Results were stratified according to treatment and to MDA achievement.

Results. Seventy-six Group 1 and 80 Group 2 subjects completed the 6-month followup. During the followup, significant changes in hemostatic and fibrinolytic variables were found in Group 1, but not in Group 2 subjects. At the end of the followup, patients treated with TNF-α inhibitors showed significantly lower levels of hemostatic and fibrinolytic variables as compared to those treated with traditional DMARD. Among Group 1 subjects, changes in hemostatic and fibrinolytic variable levels were significantly higher in those who achieved MDA versus in those who did not. Multivariate analyses showed that a treatment with TNF-α blockers affected fibrinolytic variables [plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (t-PA)] and some acute-phase proteins (D-dimer, coagulation factor VIII, and von Willebrand factor). In contrast, the MDA achievement during treatment with TNF-α blockers maximally affected fibrinolytic variables (PAI-1 and t-PA).

Conclusion. TNF-α inhibitors brought about a significant improvement of hemostatic and fibrinolytic balance in subjects with PsA. Maximal changes were found in patients achieving MDA. (First Release Feb 15 2014; J Rheumatol 2014;41:714–22; doi:10.3899/jrheum.130850)

Key Indexing Terms:
PSORIATIC ARTHRITIS HEMOSTASIS FIBRINOLYSIS MINIMAL DISEASE ACTIVITY

Subjects with rheumatic diseases such as psoriatic arthritis (PsA) and rheumatoid arthritis (RA) are highly predisposed to premature mortality from atherosclerotic vascular disease[1]. Patients with PsA exhibit an enhanced prevalence of the metabolic syndrome (MetS) and of some of its major features [obesity, hypertension (HTN), hypercholesterolemia, hypertriglyceridemia, impaired fasting glucose][2,3,4,5,6]. An association between the MetS and premature atherosclerosis is well established[7,8]. However, this association does not entirely explain the extent of premature atherosclerosis in patients with PsA[1].

Growing evidence suggests a series of mechanisms by which inflammation may act as an independent risk factor for cardiovascular disease (CVD)[1]. The hemostatic system plays a relevant role in this risk[9]. In addition to primary hemostasis (platelet function), changes in fibrinolytic [plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (t-PA)] and secondary hemostasis variables (coagulation proteins, natural anticoagulants) are known to affect the CVD risk. Impaired fibrinolysis, and/or raised levels of coagulation factors, and/or reduced levels of natural anticoagulants (protein C, protein S, antithrombin) have been recognized as major determinants of both arterial and venous thrombosis[10]. By enhancing platelet reactivity and influencing a series of coagulation and fibrinolytic

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variables, proinflammatory cytokines [i.e., tumor necrosis factor (TNF)-α and interleukin 6 (IL-6)] may trigger the thrombotic risk in patients with rheumatic diseases[11,12].

We previously reported on changes in platelet reactivity induced by TNF-α inhibitors in patients with PsA[11]. In the present study, we prospectively evaluated changes in hemostatic and fibrinolytic variables in subjects with PsA starting treatment with TNF-α inhibitors. In addition, we compared changes in these variables with those found in subjects who had achieved minimal disease activity (MDA) with traditional disease-modifying antirheumatic drugs (DMARD) and who continue to take these drugs.

MATERIALS AND METHODS

In a 24-month period (January 2010–January 2012), among subjects attending the rheumatologic outpatient clinic of the Federico II University Hospital, Naples, Italy, those with a diagnosis of PsA [according to ClASsification for Psoriatic ARthritis (CASPAR) criteria][13] were evaluated for enrollment in our study. Exclusion criteria were personal and/or family history of arterial or venous thrombosis; immunological disorders other than PsA; antiphospholipid antibodies positivity; indication to receive antiplatelet or anticoagulant treatment (atrial fibrillation, valvular diseases); conditions known to affect hemostatic variable levels (liver disease, pregnancy, malignancy, hematologic diseases, puerperium, oral contraceptive use, and hormone replacement therapy); history of chronic infectious disease (including hepatitis B and C); unstable medical conditions; and previous treatment with TNF-α blockers. Among patients with PsA who were screened for inclusion, 98 consecutive subjects who were nonresponders to the treatment with traditional DMARD and eligible to start treatment with TNF-α blockers [according to Assessment of Spondyloarthritis International Society (ASAS) recommendations][14] were enrolled as a case group (Group 1). Among those who had achieved MDA while taking DMARD and who were still successfully treated with such drugs at the time of the evaluation, 98 subjects (matched for age and sex with those of Group 1) were enrolled to serve as a control group (Group 2). According to ASAS recommendations[14], whereas subjects with PsA in Group 2 continued their treatment with traditional DMARD, those in Group 1 started treatment with TNF-α blockers. At enrollment (T0), both for cases and for controls, information about age, sex, disease duration, vascular risk factors (VRF), and previous and/or current treatments were collected as described[15].

Clinical evaluation. At enrollment, all subjects underwent a complete clinical rheumatologic and laboratory evaluation including tender joint count (TJC), swollen joint count (SJC), tender entheseal count, psoriasis area severity index (PASI), Health Assessment Questionnaire (HAQ), visual analog scale for pain (VAS), patient global disease activity VAS score, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum transaminases. Subjects were classified as having achieved MDA when fulfilling 5 of the following 7 outcome measures at 6-month followup (T1): TJC ≤ 1, SJC ≤ 1, PASI ≤ 1 or body surface area ≤ 3, VAS for pain ≤ 15, patient global disease activity VAS score of ≤ 20, HAQ ≤ 0.5, and tender entheseal points ≤ 1[16]. Otherwise, they were considered as not having achieved MDA (no-MDA).

After a 6-month followup, all subjects were reevaluated for the same clinical and laboratory variables evaluated at T0, including MDA achievement and hemostatic and fibrinolytic factor level assessment.

All subjects were also evaluated for the presence of VRF such as obesity, HTN, impaired fasting glucose, hypercholesterolemia, and hypertriglyceridemia. These were determined according to validated criteria[15].

Laboratory measures. At enrollment and after the 6-month followup, a venous blood sample was drawn from the antecubital vein of each patient without venous stasis by a 19-gauge scalp-vein needle at 8:30–9 AM after 12–15 h of overnight fasting. Blood was collected into sterile tubes containing 2 ml sterile 3.8% trisodium citrate, centrifuged at 3000×g for 15 min and the plasma samples were immediately processed. In each case, the following fibrinolytic variables were determined: PAI-1, t-PA, and the PAI-1/t-PA ratio. These hemostatic variables were determined: fibrinogen, D-dimer, coagulation factors VII and VIII (FVII and FVIII), von Willebrand factor (vWF), protein C, protein S, and antithrombin (AT).

PAI-1 and t-PA antigens (Imulyze) were measured by ELISA methods using kits from Biopool-Menarini[17]. Fibrinogen activity was evaluated by the Clauss clotting method using the kit from Mascia Brunelli. Protein C activity was evaluated by a chromogenic method using the kit from Dade-Behring. Protein S antigens (Asserachrom) were measured by ELISA methods using a kit from Diagnostica Stago, Boehringer Mannheim[18]. FVII and FVIII activity were evaluated by a clotting assay (Dade-Behring). vWF antigen was evaluated with a commercially available kit (INNOVANCE VWF Ac Kit, Siemens Healthcare Diagnostics). AT activity was measured using a commercial kit (Berichrom ATIII, Behringwerke)[19]. Levels of D-dimer were assessed with the INNOVANCE D-dimer Kit (Siemens Healthcare Diagnostics). All laboratory measurements were performed by technicians unaware of the patients' treatment and disease activity status.

The variability of laboratory methods was assessed in samples collected twice within a 1-month period from 260 subjects without any inflammatory and/or rheumatic disease, recruited in the same time period from the hospital staff. All changes in laboratory measures in patients with PsA have been adjusted for the percentage of variability of the method found in the test group.

Our study was approved by the local ethics committee of the Federico II University.

Statistical analysis. Statistical analysis was performed with the SPSS 16 system (SPSS Inc.). Continuous data were expressed as means ± SD; categorical variables were expressed as percentages. To compare continuous variables, an independent sample t-test or a 1-way ANOVA with a Bonferroni posthoc analysis was performed. The Wilcoxon test for paired samples was used as a nonparametric equivalent of the paired samples t-test used for continuous variables. These characteristics were analyzed as dichotomous (1/0) categories: abdominal obesity, hypertriglyceridemia, hypercholesterolemia, HTN, impaired fasting glucose, smoking status, and MetS. The chi-square test was used to analyze categorical data. When the minimum expected value was < 5, the Fisher's exact test was used. To adjust for all the other variables, multivariate analyses were performed with Δ-percentage changes in hemostatic and fibrinolytic variables as dependent variables, and with these also as dependent variables: age, sex, disease duration, hypercholesterolemia, hypertriglyceridemia, impaired fasting glucose, HTN, smoking habit, obesity, baseline values of hemostatic and fibrinolytic variables (FVII, FVIII, vWF, fibrinogen, D-dimer, AT, protein C, protein S, PAI-1, t-PA, PAI-1/t-PA ratio), baseline values of inflammatory reactants (ESR, CRP), Δ-percentage CRP, Δ-percentage ESR, treatment with TNF-α blockers, and the achievement of MDA. To be as conservative as possible, both unstandardized B values and standardized β values have been reported. All the results are presented as 2-tailed values with statistical significance for p values < 0.05.

Sample size evaluation. To be as conservative as possible, a sample size able to detect before-after changes in hemostatic and fibrinolytic variables > 5% (± 15 SD of the sampled population), at least 71 subjects for each arm were needed to achieve a > 80% power with a 5% α error.

RESULTS

Of the 98 subjects enrolled in Group 1, all were no-MDA at T0 and started treatment with TNF-α blockers. During the followup, 12 missing visits and 10 with missing clinical and/or laboratory values were excluded from the analysis. The remaining 76 subjects (40 females, 36 males; mean age: 45.7 ± 12.3 yrs) were analyzed. The TNF-α blockers were

adalimumab (40 mg/every 2 weeks) in 16 subjects; etanercept (50 mg/week) in 24, and infliximab (5 mg/kg every 8 weeks) in 36.

Of the 98 subjects in Group 2, all were in MDA at T0 and they continued their treatment with traditional DMARD. Of them, 18 subjects were missed at followup visits and were excluded from the study. The remaining 80 subjects (48 females, 32 males; mean age 46.6 ± 11.7 yrs) were analyzed [48 receiving methotrexate (MTX), 6 cyclosporine, 5 leflunomide, and 22 sulfasalazine]. Baseline clinical and demographic characteristics of Group 1 and Group 2 subjects are reported in Table 1. With the exception of the PAI-1/t-PA ratio, which was similar between the 2 groups, most of the variables analyzed were significantly lower in Group 2 (MDA) than in Group 1 (no-MDA).

During the 6-month treatment period with TNF-α blockers, 27 (35.5%) of the 76 subjects enrolled in Group 1 achieved MDA. All the Group 2 subjects were continuously in MDA during the same time period. Figure 1 shows that, whereas no significant changes in ESR, CRP, and hemostatic and fibrinolytic variables occurred in the Group 2, during the 6-month treatment with TNF-α blockers, both ESR and CRP significantly changed in Group 1. Hemostatic and fibrinolytic variables changed in a similar manner (Figure 1). In particular, Δ-percentage PAI ($r = 0.326$, $p = 0.004$), Δ-percentage PAI-1/t-PA ratio ($r = 0.283$, $p = 0.013$),

Table 1. Baseline clinical and demographic characteristics of case and control subjects. All measurements were performed at enrollment when all patients were using traditional disease-modifying antirheumatic drugs. Data are mean ± SD unless otherwise indicated.

Variable	Group 1 (no-MDA), n = 76	Group 2 (MDA), n = 80	p
Age, yrs	45.73 ± 12.35	46.65 ± 11.57	0.634
Male sex, n (%)	36 (47.4)	32 (40.0)	0.420
PAI-1 antigen	67.28 ± 13.94	58.62 ± 11.14	0.032
t-PA levels	9.45 ± 2.22	8.07 ± 1.61	0.027
PAI-1/t-PA ratio	7.11 ± 5.56	7.26 ± 4.87	1.000
Fibrinogen	328.57 ± 83.05	302.12 ± 43.19	0.031
D-dimer	252.12 ± 252.12	190.47 ± 73.19	0.045
FVII	123.92 ± 20.43	107.70 ± 12.18	< 0.001
FVIII	129.01 ± 25.24	119.33 ± 17.42	0.008
vWF	138.11 ± 28.41	128.98 ± 19.96	0.029
Prot C	121.47 ± 18.25	114.25 ± 14.81	0.039
Prot S	114.57 ± 23.12	106.11 ± 15.29	0.013
AT	100.43 ± 7.62	96.36 ± 5.96	0.006
ESR	22.40 ± 13.46	18.17 ± 8.98	0.032
CRP	5.02 ± 5.83	3.46 ± 2.20	0.034
Clinical subset, n (%)			
Axial + peripheral	25 (32.9)	29 (36.2)	0.596
Peripheral	27 (35.5)	26 (32.5)	0.693
Axial	18 (23.7)	19 (23.8)	1.000
Mutilans	6 (7.9)	6 (7.5)	0.780
Disease duration (mos)	126.93 ± 58.83	101.72 ± 74.01	0.004
SJC	3.39 ± 4.69	1.82 ± 2.03	0.013
TJC	14.72 ± 9.99	7.45 ± 5.58	< 0.001
PASI	1.45 ± 0.76	1.49 ± 0.68	0.700
HAQ	2.31 ± 0.52	1.20 ± 1.12	0.001
VAS	44.3 ± 21.6	22.9 ± 18.1	< 0.001
Patient global VAS	51.4 ± 23.7	23.3 ± 15.1	< 0.001
Tender entheseal count	9.66 ± 5.06	11.71 ± 5.45	0.003
Hypercholesterolemia, n (%)	38 (50.0)	47 (58.8)	0.335
Hypertriglyceridemia, n (%)	25 (32.9)	27 (33.8)	1.000
Impaired fasting glucose, n (%)	7 (9.2)	5 (6.3)	0.557
Hypertension, n (%)	14 (18.4)	18 (22.5)	0.558
Smoking habit, n (%)	22 (28.9)	17 (21.3)	0.275
Obesity, n (%)	32 (42.1)	37 (46.3)	0.631

MDA: minimal disease activity; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SJC: swollen joint count; TJC: tender joint count; PASI: psoriasis area severity index; HAQ: Health Assessment Questionnaire; VAS: visual analog scale for pain; PAI-1: plasminogen activator inhibitor-1; t-PA: tissue plasminogen activator; FVII: coagulation factor VII; FVIII: coagulation factor VIII; vWF: von Willebrand factor; AT: antithrombin; Prot C: protein C; Prot S: protein S.

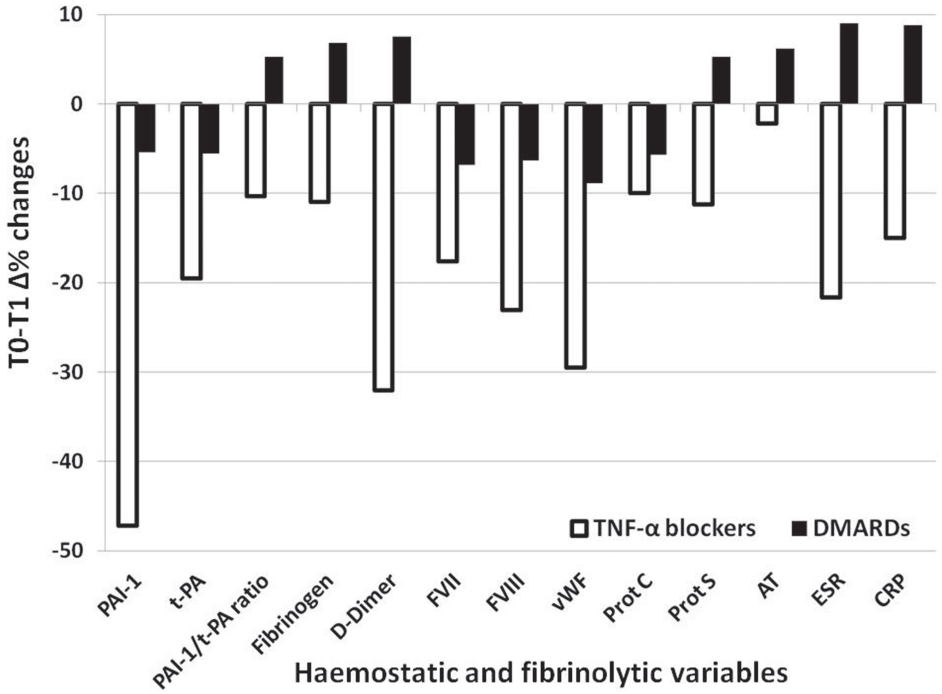


Figure 1. Δ-percentage changes of inflammatory, hemostatic, and fibrinolytic variables in Group 1 and Group 2 subjects (not head-to-head comparison). All reported Δ-percentage changes are adjusted for the percentage of method variability found in a test group. Tumor necrosis factor (TNF)-α blocker subjects (Group 1): Δ-percentage changes always $p < 0.001$ [except for Δ-percentage antithrombin (AT), $p = 0.031$]. Subjects taking disease-modifying antirheumatic drugs (DMARD; Group 2): Δ-percentage changes always $p > 0.05$. Group 1 vs Group 2: p always < 0.001 for Δ-percentage changes. PAI-1: plasminogen activator inhibitor-1; t-PA: tissue plasminogen activator; vWF: von Willebrand factor; ProtC: protein C; ProtS: protein S; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; t0: enrollment; T1: 6-month followup; FVII: coagulation factor VII; FVIII: coagulation factor VIII.

and Δ-percentage D-dimer ($r = 0.250$, $p = 0.029$) showed a direct significant correlation with Δ-percentage CRP in the Group 1 subjects, but not in those of Group 2. Of interest, whereas the effect on hemostatic and fibrinolytic variables was similar among the 3 TNF-α blockers, a trend toward a higher reduction in vWF ($p = 0.054$) and PAI-1 ($p = 0.062$) levels was found when comparing MTX with the other DMARD.

By stratifying the Group 1 population according to the achieving of MDA, Δ-percentage of hemostatic and fibrinolytic variable levels were significantly higher in those achieving MDA than in those who did not (Figure 2). Figure 3 depicts levels of hemostatic and fibrinolytic variables at the end of the 6-month followup in Group 2 as compared with Group 1 individuals. The latter are stratified according to the achievement of MDA. Of interest, those receiving TNF-α blockers (Group 1) exhibited lower values of most hemostatic and fibrinolytic variables as compared with subjects receiving traditional DMARD (Group 2), this difference being maximal in Group 1 patients achieving MDA.

To address the relationship between inflammation and changes in hemostatic and fibrinolytic variables, when the Group 1 population was stratified according to Δ-percentage CRP tertiles, progressively higher Δ-percentage changes in hemostatic and fibrinolytic variables were found for increasing Δ-percentage CRP tertiles (Figure 4). Further refining these results, in a linear regression model, after adjusting for all the other variables, Δ-percentage CRP significantly predicted changes in PAI-1 ($\beta = 0.691$, $p < 0.001$), in t-PA ($\beta = 0.326$, $p = 0.004$), and in D-dimer ($\beta = 0.233$, $p = 0.008$).

These same multivariate analyses, when performed in Group 2 patients, did not yield any significant result.

In multiple linear regression analyses on the whole study sample (Groups 1 and 2), the treatment with TNF-α blockers determined significantly higher changes in hemostatic and fibrinolytic variables as compared to those found in subjects continuously treated with traditional DMARD (Figure 5A).

Specifically analyzing subjects receiving a treatment with TNF-α blockers (Group 1), the MDA achievement was a predictor of higher changes in hemostatic and fibrinolytic variables as compared with no-MDA status (Figure 5B).

Overall, results of these multivariate analyses showed that a 6-month treatment with TNF-α blockers affected fibrinolysis variables (PAI-1 and t-PA) as well as some

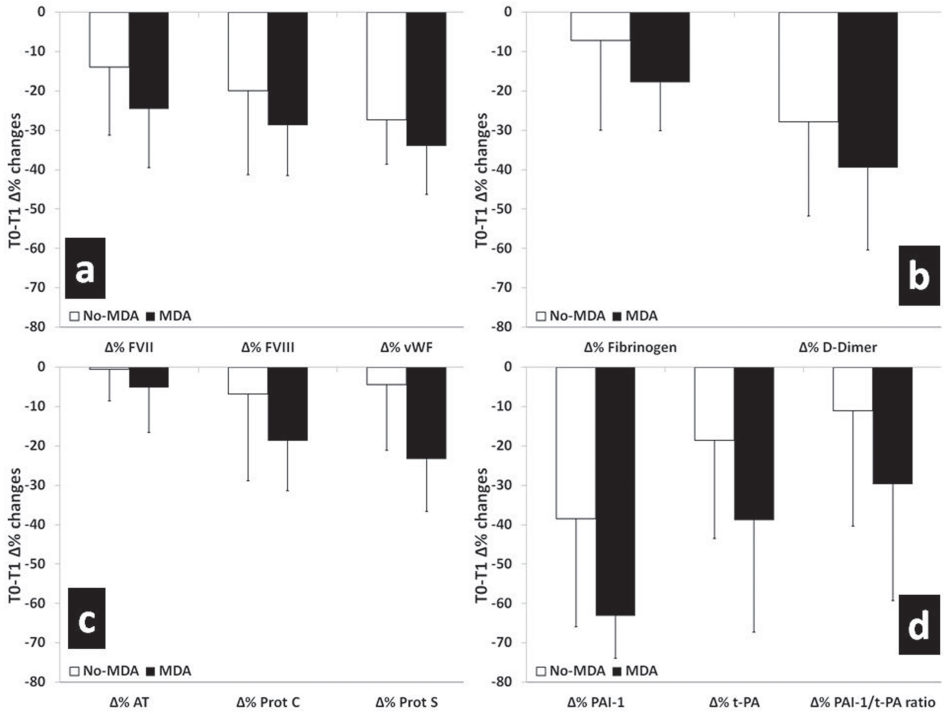


Figure 2. Δ-percentage changes in coagulation factors (panels A and B), in natural anticoagulants (panel C), and in fibrinolytic variables (panel D) during a 6-month treatment with tumor necrosis factor-α. Stratification of Group 1 population is according to achievement of minimal disease activity (MDA). P value always < 0.05. All reported Δ-percentage changes are adjusted for the percentage of method variability found in a test group. vWF: von Willebrand factor; AT: antithrombin; Prot C: protein C; Prot S: protein S; PAI-1: plasminogen activator inhibitor-1; t-PA: tissue plasminogen activator; t0: enrollment; T1: 6-month followup; FVII: coagulation factor VII; FVIII: coagulation factor VIII.

acute-phase proteins (D-dimer, FVIII, and vWF). In contrast, the MDA achievement during treatment with TNF-α blockers maximally affected fibrinolytic variables (PAI-1 and t-PA).

Of interest, the same results were confirmed when analyzing standardized β values (Figure 5).

After the 6-month followup evaluation, of the 49 patients with a poor response to TNF-α blockers, 31 changed type of TNF-α blocker and 18 added nonsteroidal antiinflammatory drugs to the ongoing treatment, and in line with results of a recent study[20], entered a customized rehabilitative program.

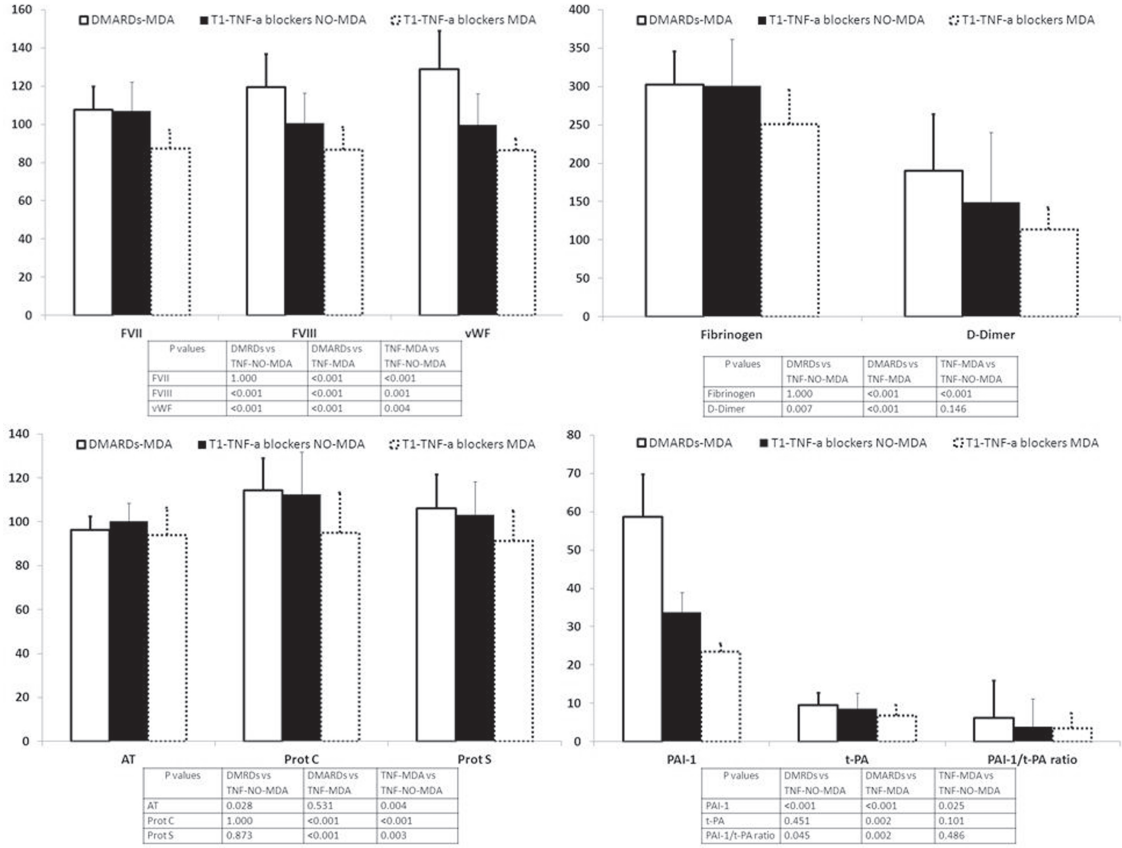
DISCUSSION

Our prospective study provides evidence about the link between inflammation and thrombotic risk. In particular, we documented that control of the inflammatory process is associated with a significant improvement in hemostatic and fibrinolytic variables in subjects with PsA, with maximal changes being documented in patients achieving MDA. These variables have been found to predict arterial and venous thrombosis, which are major complications in PsA[21]. Previous studies have shown that the overproduction of proinflammatory cytokines (TNF-α, IL-6), besides playing a crucial role in the inflammatory process correlated with rheumatic disease activity[22], is also involved in the modulation of the fibrinolytic system[23].

The total fibrinolytic potential of human blood is determined by the balance between t-PA and PAI-1[23]. TNF-α has proved to be a potent agonist of PAI-1 expression and regulation[24]. In addition, high plasma levels of prothrombin fragment 1 + 2 and of D-dimer (markers of thrombin activation and of fibrinolysis, respectively) have also been found in patients with RA[25]. Thus, by inducing a procoagulant shift in the hemostatic balance, chronic inflammation promotes fibrin generation and in turn, thrombosis[26,27].

At variance with all the other previous studies, which exclusively focused on patients with RA, we have extended the evaluation of global hemostasis changes to patients with PsA.

Besides the evaluation of fibrinolytic balance, we reported changes in a series of other hemostatic factors. In detail, vWF, FVIII, and FVII are recognized acute-phase proteins, increasing in the presence of inflammation, cancer, and pregnancy[28] and leading to a prothrombotic state and to an increased risk of venous and arterial thrombosis[29]. Moreover, protein C and protein S are natural anticoagulant proteins that play a major role in opposing hypercoagulable



P values	DMRDs vs TNF-NO-MDA	DMARDs vs TNF-MDA	TNF-MDA vs TNF-NO-MDA
FVII	1.000	<0.001	<0.001
FVIII	<0.001	<0.001	0.001
vWF	<0.001	<0.001	0.004

P values	DMRDs vs TNF-NO-MDA	DMARDs vs TNF-MDA	TNF-MDA vs TNF-NO-MDA
Fibrinogen	1.000	<0.001	<0.001
D-Dimer	0.007	<0.001	0.146

P values	DMRDs vs TNF-NO-MDA	DMARDs vs TNF-MDA	TNF-MDA vs TNF-NO-MDA
AT	0.028	0.531	0.004
Prot C	1.000	<0.001	<0.001
Prot S	0.873	<0.001	0.003

P values	DMRDs vs TNF-NO-MDA	DMARDs vs TNF-MDA	TNF-MDA vs TNF-NO-MDA
PAI-1	<0.001	<0.001	0.025
t-PA	0.451	0.002	0.101
PAI-1/t-PA ratio	0.045	0.002	0.486

Figure 3. Levels of hemostatic/fibrinolytic factors in subjects treated with disease-modifying antirheumatic drugs (DMARD) and in those receiving tumor necrosis factor (TNF)-α treatment after 6-month followup. Stratification according to disease activity. MDA: minimal disease activity; T1: 6-month followup; vWF: von Willebrand factor; PAI-1: plasminogen activator inhibitor-1; Prot C: protein C; Prot S: protein S; AT: antithrombin; t-PA: tissue plasminogen activator; FVII: coagulation factor VII; FVIII: coagulation factor VIII.

states[18]. Consistent with the link between natural anticoagulants and variables involved in hypercoagulable states, changes we have reported in protein C and protein S level are likely to be related to the changes that occurred in PAI-1 and t-PA levels.

This is also the first study, to our knowledge, prospectively comparing the effects induced by TNF-α inhibitors and by traditional DMARD on secondary hemostasis variables. Indeed, the contemporaneous evaluation of a group of subjects continuously treated with traditional DMARD allowed for a comparison of the effects of traditional and biologic antirheumatic drugs on hemostatic variables.

In line with previous studies[30], at the baseline evaluation (Table 1), by assessing the effect of inflammation and of disease activity on hemostatic and fibrinolytic variables, we found that most of these variables were significantly higher in patients with active disease (Group 1) than in those with minimal disease activity (Group 2). Of interest, because all subjects were under DMARD at the time of the baseline assessment, we are confident to have evaluated the effect of disease activity on hemostatic and fibrinolytic balance.

In addition to traditional DMARD, treatment with TNF-α inhibitors improved clinical and laboratory measures of disease activity in rheumatic diseases and reduced local and systemic inflammation[12,23]. Besides the control of inflammation, TNF-α inhibitors have been found to downregulate fibrinolytic[23,31] as well as hemostatic[12] variables and to normalize platelet hyperreactivity[11], thus leading to a reduction in the CV risk[21,32].

We found that, at the end of the 6-month followup, as compared with those continuously treated with DMARD, those starting a treatment with TNF-α blockers showed a significant reduction in hemostatic and fibrinolytic variables. In addition, maximal changes in coagulation variables were found in those achieving the MDA during the TNF-α blocker treatment. In keeping with this, for increasing changes in CRP levels, a progressively higher variation in all evaluated variables was found.

For comparison purposes, inflammatory markers and hemostatic/fibrinolytic variables did not change in the group of patients who continued to receive traditional DMARD (all changes < 10% from baseline).

In addition, with the exception of AT levels, patients

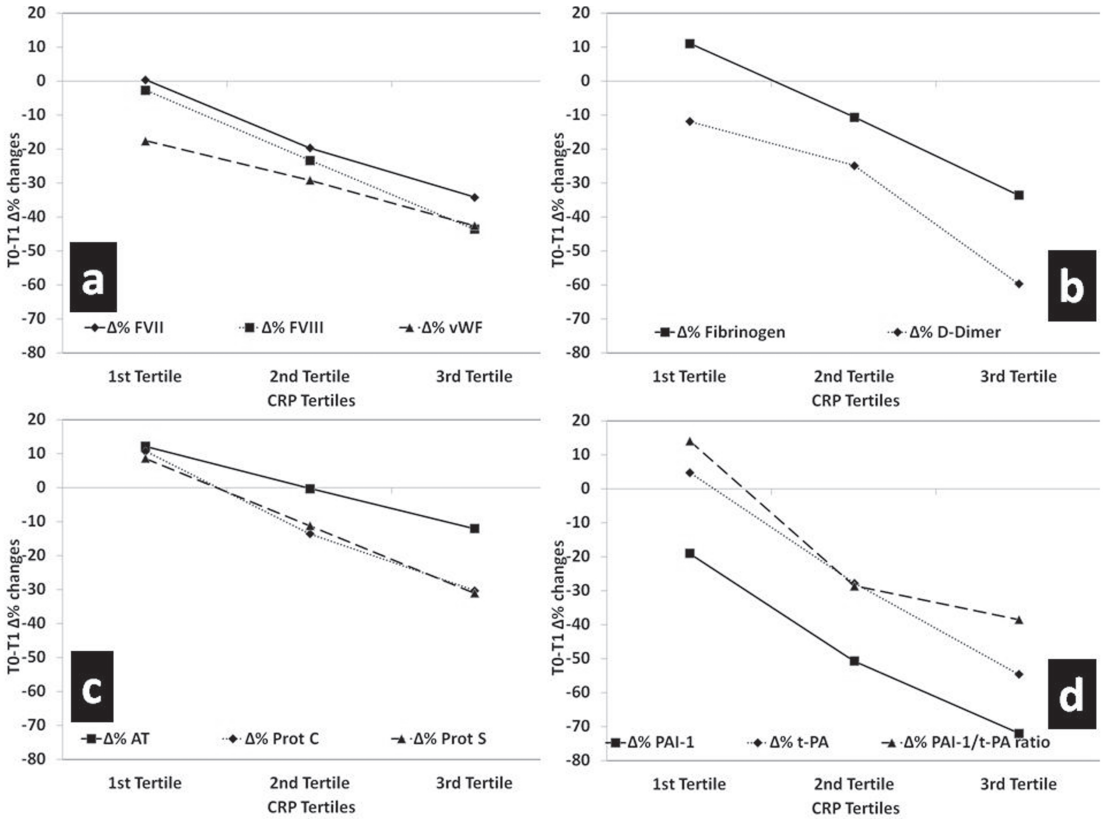


Figure 4. Δ-percentage changes in hemostatic and fibrinolytic variables according to Δ-percentage C-reactive protein (CRP) tertiles. Group 1 population. All reported Δ% changes are adjusted for the percentage of method variability found in a test group. First Δ-percentage CRP tertile (< 19%): n = 25, mean Δ-percentage CRP: 8.09 ± 3.44. Second Δ-percentage CRP tertile (19-50%): n = 26, mean Δ-percentage CRP: 25.58 ± 5.60. Third Δ-percentage CRP tertile (> 50%): n = 25, mean Δ-percentage CRP: 52.04 ± 13.98. T0: enrollment; T1: 6-month followup; vWF: von Willebrand factor; AT: antithrombin; Prot C: protein C; Prot S: protein S; PAI-1: plasminogen activator inhibitor-1; t-PA: tissue plasminogen activator; FVII: coagulation factor VII; FVIII: coagulation factor VIII.

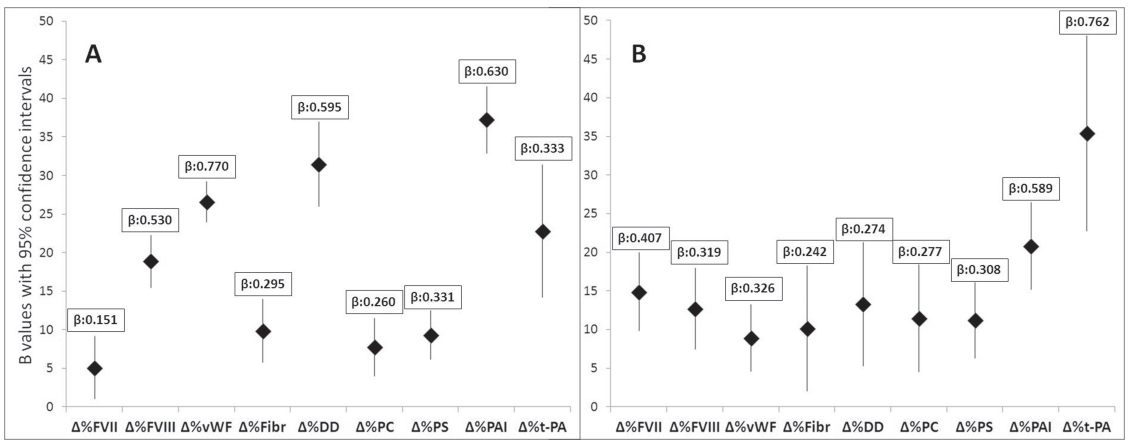


Figure 5. Multivariate analysis (linear regression model) for the prediction of changes in hemostatic and fibrinolytic variables. A. Effect of the treatment with tumor necrosis factor (TNF)-α blockers versus traditional disease-modifying antirheumatic drugs (DMARD) in the whole study sample (Group 1 and Group 2, not head-to-head comparison). B. Effect of minimal disease activity (MDA) achievement versus no-MDA status in subjects receiving TNF-α blockers (Group 1). In both models, prediction of antithrombin and PAI-1/t-PA ratio was not significant (p always > 0.05). Estimated B regression coefficients give, for each of the explanatory variables, the predicted Δ-percentage change in each variable in the presence of the explanatory variable (treatment with TNF-α blockers and achieving MDA for panels A and B, respectively). The analysis of standardized β coefficients, which provides values adjusted for all the other explanatory variables, confirmed similar results. Patients of Group 2 were excluded from the analysis reported in panel B because in that population, the MDA was a constant. vWF: von Willebrand factor; DD: D-dimer; PC: protein C; PS: protein S; PAI: plasminogen activator inhibitor; t-PA: tissue plasminogen activator; FVII: coagulation factor VII; FVIII: coagulation factor VIII.

taking DMARD had higher levels of hemostatic and fibrinolytic factors when compared to anti-TNF patients (both to those achieving MDA and to those with persistent active disease). This finding suggests the possibility that the mechanism of action of TNF-α inhibitors on hemostatic and fibrinolytic variables does not depend only on the successful control of inflammation (MDA achievement). However, this issue cannot be ruled out, and further data are needed to understand whether improvements in hemostatic and fibrinolytic variables are only correlated to reduction of inflammatory status.

Some potential limitations of our study need to be addressed. Whereas patients treated with TNF-α blockers were enrolled before starting this treatment and were prospectively followed, those taking DMARD were already being treated with these drugs before the study start. To better compare the effects of the 2 drug categories on global hemostasis variables, a randomized design would be better. However, because of current guidelines about the indication for TNF-α blocker treatment[14], biologic drugs can be started only after a failure of DMARD. In turn, for ethical reasons, subjects experiencing a failure of traditional treatment cannot be continuously treated with DMARD. However, our study provided some relevant data about changes in hemostatic and fibrinolytic variables when patients taking DMARD are switched to TNF-α blockers.

In patients taking DMARD, an interesting finding is that MTX showed a trend toward a higher efficacy in the reduction of some hemostatic and fibrinolytic variables as compared to other DMARD. However, given the relatively small sample size, no further stratifications were reliable, and further data are needed to address this issue.

A further relevant point is that traditional CV risk factors, in particular obesity, are known to affect hemostatic and fibrinolytic balance[33]. On the other hand, the interrelationship between cardiometabolic factors (mainly obesity) and chronic inflammation is being studied[34,35,36]. Accordingly, to avoid any potential source of bias, and to specifically evaluate effects of the antirheumatic treatment on hemostatic and fibrinolytic balance, all results have been adjusted for the presence of major CV risk factors and their changes during the followup.

Our study confirms the role of TNF-α inhibition in the reduction of systemic inflammation, with a significant improvement in the global hemostatic and fibrinolytic balance of patients with PsA. These data, extending and confirming results obtained on carotid atherosclerosis, hepatic steatosis, and platelet reactivity[11,21,32,37], suggest potential cardioprotective effects of TNF-α inhibitors. Whether this is a drug-specific effect or a consequence of the inflammatory process control is unclear to date and cannot be determined based on the present data.

Further studies evaluating risks (side effects)[38] and benefits (antiinflammatory and cardioprotective effects) of treatment with TNF-α inhibitors are needed to allow for a tailored antirheumatic treatment choice.

APPENDIX 1.

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