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Low sCD163/TWEAK Ratio at First Day After Acute Myocardial Infarction Associated with Adverse Cardiac Remodeling in Non-Elderly Patients

Aim	In this study, we aimed to investigate the role of sCD163/tumor necrosis factor-like weak apoptosis-inducing (TWEAK) ratio in cardiac remodeling in non-elderly patients diagnosed with first acute myocardial infarction (MI).
Material and Methods	Forty-four patients (age ranges: 40–64 years) diagnosed with first-time acute ST-elevation MI in the emergency department were evaluated with cardiac magnetic resonance (CMR) imaging. Adverse remodeling (AR) was defined the increases of left ventricular end-diastolic volume by ≥12% by CMR at 6-month post-MI TWEAK and sCD163 were measured at the first day (baseline), 2 weeks and 6 weeks post-MI.
Results	The average age of patients included in the study was 53.6±5.1 years. AR was detected in 18 patients at the 6 months post-MI. At the first day post-MI, median sCD163 concentration (116 069 vs 86 394 pg/mL, p=0.040) and median TWEAK concentration (759.4 vs 220.1 pg/mL, p<0.001) were higher in AR group compared to group without AR (the non-AR group), median sCD163/TWEAK ratio (101.4 vs. 406.8; p<0.001) was lower. At the first day post-MI, concentrations of TWEAK and sCD163 showed a positive correlation in AR group and group without AR s. At 2 weeks post-MI, positive correlation continued in the non-AR group, but no significant correlation was found in the AR group. At the first day post-MI, sCD163/TWEAK ratio was higher diagnostic performance compared to TWEAK and sCD163.
Conclusion	In the early phase post-MI, the relationship between sCD163 – TWEAK may have an important role in AR pathogenesis. A lower sCD163/TWEAK ratio on the first day after MI was associated with an increase in left ventricular end-diastolic volume after 6 months of follow-up.

Keywords	Inflammation; sCD163; myocardial infarction; TWEAK; cardiac remodeling
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Introduction

Cardiac remodeling is one of the major reasons for heart failure following acute myocardial infarction (MI) [1]. Cardiac remodeling starts with tissue damage and necrosis in the post-MI period with subsequent inflammation and infiltration by immune cells. This is followed by resolution of the inflammation characterized by myofibroblast proliferation, scar formation, and neovascularization [2, 3]. Unfavorable histopathological changes result in permanent, incompatible differentiation along with structural and functional cardiac impairment and adverse remodeling (AR) [4, 5].

Tumor necrosis factor-like weak inducer of apoptosis (TWEAK) is a member of the TNF superfamily that contributes to the pathogenesis of cardiac remodeling by participating in various biological activities. These include proliferation, migration, differentiation, apoptosis, angiogenesis, and inflammation. TWEAK's mechanism of action is carried out by interaction with endothelia, smooth muscle cells, cardiomyocyte cell lines, and cardiac fibroblasts [6, 7].

CD163 is expressed by monocytes/macrophages, and it removes TWEAK from the site of injury. As a TWEAK scavenger, CD163 prevents its harmful biological effects [8]. CD163 interacts in vivo with TWEAK to regulate tissue regeneration following ischemic damage [9]. However, the interactions of soluble CD163 (sCD163) and TWEAK in myocardial healing after acute MI remain unclear. In addition, elderly MI patients are especially at risk for adverse cardiac remolding and poor survival in the post-MI period. However, in this study, we investigated the role of the sCD163/TWEAK ratio in cardiac remodeling in non-elderly patients diagnosed for the first time with acute MI.

Material and Methods

This study was a multi-center prospective study conducted between June 2015 and June 2018 at Ankara Dr. Nafiz Korez Sincan State Hospital, Ankara Diskapi Training and Research Hospital, Yildirim Beyazit University Atatürk Training and Research Hospital, and Ankara Numune Training and Research Hospital. Assuming an alpha of 0.05, a power of 0.80, and with 30% estimated AR rate consistent with previous reports, the estimated sample size was at least 40 patients. The local ethics committee approved the study protocol, and signed informed consent forms were obtained from all patients enrolled in the study.

Study Population

295 patients who were admitted to the emergency department with first-time ST-elevation myocardial infarction (STEMI) were considered for the study. Inclusion criteria: 1) more 18 yrs of age, 2) presented within the first 12 hr after the onset of chest pain that had been ongoing for more than 30 min, 3) with > 0.1 mV ST-segment elevation in at least two or more related leads, 4) underwent primary percutaneous coronary intervention. The definition of STEMI was according to the 3rd universal definition of MI [10], and STEMI was managed according to the latest European Society of Cardiology guidelines [11]. To prevent effects of daily rhythm on the expression differences of inflammatory markers, only patients who were admitted early in the day (08:00–12:00) were included in the study.

To eliminate the possible effects of advanced age, geriatric patients were excluded. Other exclusion criteria: 1) patients in cardiogenic shock or in need of an intra-aortic balloon pump, 2) a history of silent ischemia/infarct, 3) right coronary artery occlusion, 4) moderate to severe valvular disease, 5) any kind of systemic inflammatory disease, autoimmune diseases, or a history of chronic corticosteroid or anti-inflammatory drugs, 6) those who were pregnant, had given birth within the last 90 days, or were breastfeeding, 7) patients for whom an emergency or elective coronary artery bypass graft was planned after the angiography procedure, 8) post MI myocardial ischemia, recurrent events (i.e., recurrent MI or coronary revascularization) post-MI. After applying the inclusion and exclusion criteria, the remaining 44 patients were enrolled in the study.

The clinical, demographic, laboratory, and radiological findings were recorded in a timely manner in the patients' files at presentation and during follow-up examinations. The Global Registry of Acute Cardiac Events (GRACE) risk score was calculated (www.gracescore.org).

Laboratory Analysis

Blood samples were obtained from the antecubital vein at presentation for troponin and a lipid panel, and again at the first day, at 2 wks, and at 6 wks follow-up for cytokine markers. Blood samples were centrifuged at 1500 rpm for 10 min and stored at –80 °C. Results were studied after all samples were collected and then analyzed in the same laboratory, by the same laboratory technician, in a single session, with the same device. Total cholesterol was determined by a homogeneous enzymatic colorimetric method with a Hitachi Modular P800 autoanalyzer (Roche Diagnostics Corp., Indianapolis, IN, USA). Low-density lipoprotein was calculated according to the Friedewald method [12]. Cytokines were analyzed in duplicate. Serum and plasma samples were thawed on ice and concentrations of TWEAK and sCD163 were analyzed according to the manufacturer's instructions for the bead-based multiplex immunoassay system (171-AL001M, Bio-Plex Pro™ Human Inflammation Panel 1, 37-Plex). The formation of different sandwich immunocomplexes on distinct bead sets was measured and quantified using the Bio-Plex® MAGPIX™ System (Bio-Rad Laboratories, Hercules, CA, USA). The final concentration was calculated with the Bio-Plex Manager v5.0 software package (Bio-Rad). The assay working range for sCD16 and TWEAK is as follows; lower limit of quantification (LLOQ) 1338 pg/ml and 3.1 pg/ml, upper limit of quantification (ULOQ) 975 916 pg/ml and 6 772 pg/ml, assay sensitivity (LOD) 16.8 pg/ml and 0.5 pg/ml.

Cardiac Magnetic Resonance Imaging

Cardiac MRI was performed for all patients in the 2nd wk and in the 6th month. Evaluation of cardiac remodeling was performed with a 3-T MRI scanner (Magnetom Skyra, Siemens Medical Systems, Erlangen, Germany). One 4-chamber view, cine short-axis sections (slice thickness of 6 mm at 10-mm intervals), and one 2-chamber view were acquired. Imaging parameters were as follows: echo time 1.42 ms, repetition time (TR) 39 ms, flip angle 57°, voxel size 1.67 × 1.67 × 6 mm. MRI data were transferred to the workstation. The markers of left ventricular (LV) systolic function were assessed by using the retrospective electrocardiogram-

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Table 1. Change of cytokines concentrations according to follow-up times

Variables	Adverse Remodeling		p_1	p_2
	No, n=26	Yes, n=18		
sCD163, pq/ml				
First day	86 394 (70 114–122 711)	116 069 (82 092–154 971)	0.040*	0.048*
2 wk	139 870 (117 092–212 170)	125 775 (100 603–168 167)	0.181	
6 wk	121 405 (95 228-152 880)	129 932 (112 147-161 298)	0.793	
TWEAK, pq/ml				
First day	220.1 (170–281.7)	759.4 (342.9–972.9)	<0.001*	<0.001*
2 wk	358.7 (288.8–382.1)	276.1 (208.4–297.6)	0.008*	
6 wk	269.2 (235.8–377.5)	274.1 (240–311.7)	0.583	
sCD163/TWEAK ratio				
First day	406.8 (343.7–544.8)	101.4 (78–209.8)	<0.001*	<0.001*
2 wk	404.8 (353.7–498.3)	489.5 (372.4–572.2)	0.364	
6 wk	434.0 (367.5–535)	478.0 (371–611.7)	0.417	

* p <0.05.
p_1: In post-MI periods, comparison of the cytokines concentrations in AR group vs non-AR group. p_2: Change of cytokines concentrations at the post-MI periods AR group vs non-AR group. Abbreviations: sCD163, soluble CD163, TWEAK, tumor necrosis factor-like weak inducer of apoptosis. Data are median (IQR).

gated turbo-fast low-angle shot (turbo-FLASH) sequence. The LV end-diastolic volume (EDV) and LV end-systolic volume (ESV) were measured with a Siemens syngo.via VA30. The LVEDV and LVESV were calculated with short-axis based planimetry from the basal to apical level. The LV stroke volume was calculated as LV EDV–LV ESV, and ejection fraction (EF) was calculated as follows: EF= [(LV EDV–LV ESV)/LV EDV] × 100. The definition of AR was based on ≥12% increase in LV EDV and LV ESV at 6 mos [13]. Accordingly, patients were divided into two groups as AR and non-AR.

Statistical Analysis

Statistical analysis was performed by using SPSS 20 for Windows (IBM Corp., Armonk, NY, USA). Normal distribution of data was evaluated by the Kolmogorov–Smirnov test. Numeric variables with and without normal distribution were plotted as mean ± standard deviation and median (interquartile range: IQR), respectively. Categorical variables are indicated as numeric and percentile values. The Student T-test or Mann–Whitney U test was used for the comparison of numeric variables according to the distribution between the two groups. Chi-square, Yates correction, and Fischer absolute chi-square tests were used for comparison of categorical data. Mixed model for repeated measures analysis was performed for comparison of cytokine concentrations in the post-MI period and during follow-up. In the post-MI period, the effect of cytokine concentrations on AR was examined with logistic regression analysis models. Model I regression analysis included cytokine concentrations measured on first day post-MI. Model II included changes in cytokine concentrations from first day to 2 wks post-MI. Model III included changes in cytokine concentrations from first day to 6 wks post-MI. All logistic regression models were adjusted for age, sex, and smoking, comorbidities, symptom to balloon time, infarct size, serum troponin concentrations and CRP concentrations and cardiac output. In logistic regression models, the proportion of the total variation of the dependent variable can be explained by independent variables was shown by the Nagelkerke R2. Diagnostic performance was evaluated by ROC curve analysis. Values of p<0.05 (indicated by *) were considered statistically significant.

Results

The mean age of patients with first-time STEMI was 53.6±5.1 years, and the majority were male (88.6%). 18 patients (40.9%) had hypertension and 19 (43.2%) had a history of smoking. AR was detected in 18 patients at 6 mos post-MI (the AR group). There were no significant differences in demographic, laboratory and CMR baseline findings in the AR group compared to the group without AR (the non-AR group. n=26). At 6 mos post-MI, mean LVEF was lower (43.4±11.2 vs 51.4±8.6%, p=0.011) and mean LVEDV (189.7±32.4 vs 145.9±32.9 ml, p<0.001) and median LVESV (119.5 vs 72.5 ml, p=0.004) were higher in the AR group. Detailed demographic, laboratory, and clinical findings at the time of admission of the study population are shown in Supplementary Table 1.

On first day post-MI, the median sCD163 concentration (116069 vs 86394 pg/ml, p=0.040) and the median TWEAK concentration (759.4 vs 220.1 pg/ml, p<0.001) were higher in the AR group compared to the non-AR group, but the median sCD163/TWEAK ratio (101.4 vs. 406.8; p<0.001) was lower. At 2 wks post-MI, the median TWEAK concentration were higher in the AR group compared to the non-AR group, while the median sCD163 concentration and the sCD163/TWEAK ratios were not significantly different. At 6 wks post-MI, the median sCD163 and TWEAK concentrations, and the sCD163/TWEAK ratios were not significantly different in the AR and non-AR groups (Table 1).

In the AR group, the sCD163 concentration was not significantly different in the post-MI periods. In the non-AR group, the sCD163 concentration was higher at 2 wks

compared to the first day post-MI, whereas no significant differences were found at 6 wks compared to 2 wks post-MI. In the AR group, the TWEAK concentration was lower at 2 wks compared to the first day post-MI, whereas no significant differences were evident at 6 wks compared to 2 wks post-MI. In the non-AR group, the TWEAK concentration was higher at 2 wks compared to the first day post-MI, but it was lower at 6 wks compared to 2 wks post-MI (Table 1).

On the first day post-MI, the concentrations of TWEAK and sCD163 were positively correlated in the AR (r= 0.719, p<0.001) and non-AR groups (r=0.532, p=0.005). At 2 wks post-MI, this positive correlation continued in the non-AR group (r=0.553, p=0.003), but no significant correlation was present in the AR group (r=0.230, p=0.211) (Table 2).

In the AR group, there was a positive correlation between infarct size at 2 wks post-MI, and the TWEAK (r=0.450, p<0.001) and sCD163 (r=0.331, p=0.008) concentrations on the first day post-MI, while a negative correlation was found for the TWEAK/sCD163 ratio (r= –0.490, p<0.001). Similar findings were found in non-AR group (relationships with infarct size; TWEAK, r=0.306, p=0.037; sCD163, r=0.295, p=0.049, and TWEAK/sCD163 ratio, r= –0.328, p=0.011). At the 2 and 6 wks of post-MI, no such correlations were found with infarct size.

The effect of demographic and clinical findings on the development of adverse remodeling is shown in Supplementary Table 2. At the first day post-MI, high TWEAK and sCD163 concentrations and low sCD163/TWEAK ratio were related to AR in the adjusted regression model. In addition, the regression model in which changes in post-MI cytokine concentrations (Model II and Model III) were included showed that decreases in TWEAK and CD163 concentrations and an increase in the sCD163/TWEAK ratio were related to AR (Table 3). Model I was found to better explain the total variation of AR development compared to other regression models (for Nagelkerke R2: Model I=0.715 vs Model II=0.566 vs Model III=0.531).

The diagnostic performance of TWEAK, CD163, and the sCD163/TWEAK ratio according to post-MI periods is showed in Supplementary Table 3. At the first day post-MI, sCD163/TWEAK ratio had a higher diagnostic value compared to TWEAK and sCD163. The change of the sCD163/TWEAK ratio showed its superior diagnostic value compared to changes of TWEAK and sCD163 concentrations during the post-MI periods. The diagnostic value of the sCD163/TWEAK ratio at the first day post-MI, and changes of the sCD163/TWEAK ratio did not differ in predicting AR (Figure 1).

Table 2. Correlation between TWEAK and sCD163 according to the post-MI period

Adverse remodeling	sCD163	Correlation	TWEAK		
			First day	2 wks	6 wks
No, n=26	First day	r	0.532	–	–
		p	0.005*	–	–
	2 wk	r	0.503	0.553	–
		p	0.009*	0.003*	–
	6 wk	r	0.065	–0.108	0.506
		p	0.752	0.600	0.008*
Yes, n=18	First day	r	0.719	–	–
		p	<0.001*	–	–
	2 wk	r	0.294	0.230	–
		p	0.187	0.211	–
	6 wk	r	0.216	0.053	0.304
		p	0.315	0.836	0.221

sCD163, soluble CD163; TWEAK, tumor necrosis factor-like weak inducer of apoptosis.

Table 3. Adjusted logistic regression analysis of the effects of cytokines on adverse cardiac remodeling

Model	Cytokines	Adjusted Univariable		
		OR	95% CI, Lower; upper	p
Model I	sCD163	1.08	1.01–1.16	0.030*
	TWEAK	3.09	1.30–7.25	0.011*
	sCD163/TWEAK ratio	0.97	0.95–0.99	<0.001*
		Nagelkerke R2=0.715, p<0.001		
Model II	sCD163	0.98	0.97–0.99	0.035*
	TWEAK	0.93	0.88–0.98	0.020*
	sCD163/TWEAK ratio	1.04	1.01–1.07	0.012*
		Nagelkerke R2=0.566, p<0.001		
Model III	sCD163	0.96	0.93–0.99	0.049*
	TWEAK	0.97	0.95–0.99	0.035*
	sCD163/TWEAK ratio	1.04	1.02–1.07	0.011*
		Nagelkerke R2=0.531, p<0.001		

* p<0.05. Reference group: without adverse remodeling.
All analyses were adjusted for age, sex, and smoking, comorbidities, symptom to balloon time, infarct size, serum troponin concentrations, CRP concentrations, and cardiac output.
Model I included cytokine concentrations measured on first day post-MI. Model II included changes in cytokine concentrations from first day to 2 wks post-MI. Model III included changes in cytokine concentrations from first day to 6 wks post-MI.
CD163, soluble CD163; TWEAK, tumor necrosis factor-like weak inducer of apoptosis; OR, odds ratio; CI, confidence interval.

Discussion

This study, to the best of our knowledge, is the first study to evaluate the predictive value of the post-MI sCD163/TWEAK ratio in non-geriatric STEMI patients. We excluded elderly MI patients who are at risk of adverse cardiac remodeling in the short and long terms. We found high TWEAK and sCD163 concentrations at the first day post-MI in the AR group. While there was a positive correlation between TWEAK and sCD163 concentrations at the first day post-MI in the AR and non-

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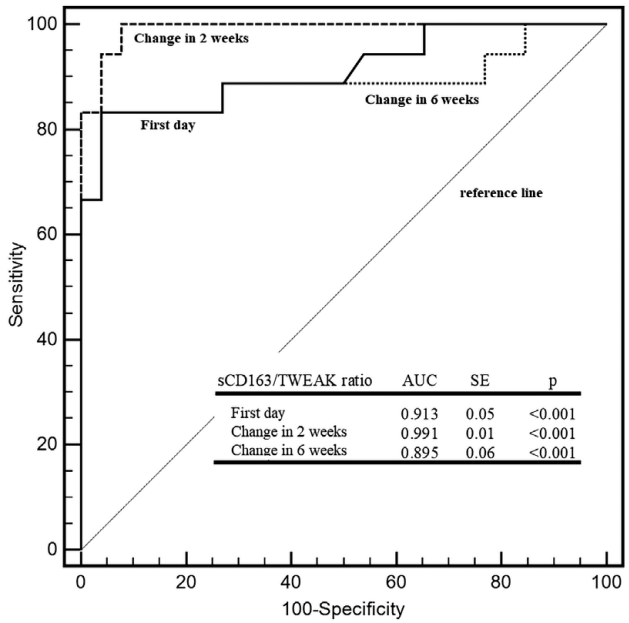
Figure 1. Diagnostic performance of the sCD163/TWEAK ratio in predicting adverse cardiac remodeling



AR groups, the correlation between TWEAK and sCD163 concentrations at 2 wks post-MI was not significant in the AR group. The sCD163/TWEAK ratio was found to be a more valuable predictive parameter for the development of AR than the concentrations of TWEAK and sCD163.

Adverse cardiac remodeling post-MI is a process of regional and global structural and functional changes as a consequence of some mechanisms that include an exaggerated inflammatory response. During the remodeling process, the expression of pro- and anti-inflammatory cytokines is enhanced in the myocardium [14]. Experimental studies showed that TWEAK concentration is upregulated in cardiomyocytes during the post-MI period, and this has negative effects on cardiac repair [12, 15, 16]. Negative effects of TWEAK on cardiac repair are explained by mechanisms that include attenuation of metabolic adaptation and an increase in cardiac load by inhibition of peroxisome proliferator-activated receptor gamma co-activator 1-alpha [12], or by triggering of macrophage infiltration leading to cardiac fibrosis [15].

There is an increase in TWEAK in all tissues with ischemic damage. Here the parameter that determines better recovery seems to be sCD163, which has an important role in regulating tissue regeneration after ischemic injury. CD163 was first identified as a macrophage-specific scavenger for hemoglobin – haptoglobin complexes that protect tissues from oxidative damage and inflammation. The harmful effects of TWEAK are balanced by the increase in sCD163, since, upon binding to CD163-expressing macrophages, TWEAK is internalized and degraded [17, 18]. At the first day post-MI, higher TWEAK and sCD163 concentrations were found in the AR group than in the non-AR group. At 2 wks post-MI, higher TWEAK and sCD163 concentrations were found in the non-AR group, and a positive correlation between TWEAK and sCD163 was detected. These findings suggest that a mismatch between the TWEAK and sCD163 concentrations, as in the 2 wk post-MI in AR patients, causes CD163 to be unable to effectively neutralize the adverse effects of TWEAK. Thus, the association of TWEAK with poor cardiac repair may contribute to AR.

Evaluation of TWEAK and CD163 interactions is more important in terms of prognosis [19]. Additionally, the sCD163/TWEAK ratio is a more sensitive atherosclerosis marker than sCD163 or TWEAK concentrations, and the interaction between TWEAK and CD163 may play an important role in vivo [8]. TWEAK can directly activate fibroblast functions, and an in vitro study supports that its inhibition by sCD163 may have anti-fibrotic effects [20–22]. The sCD163/TWEAK ratios were lower at the first day post-MI in the AR group, while in the non-AR group it remained stable in the post-MI periods. Moreover, in the non-AR group, during the 2 wks follow-up period, there was a positive correlation between TWEAK levels and sCD163 levels. These findings suggest that consistent and positive patterns of sCD163 and TWEAK interactions can be associated with better cardiac repair.

Another striking finding of our study was the determination of the specific period during which sCD163/TWEAK ratios contributed to adverse cardiac remodeling. sCD163/TWEAK ratios were similar at the 2 wks and 6 wks post-MI in patients with and without AR. However, at the first day post-MI, the sCD163/TWEAK ratio showed better diagnostic value compared to both components and to other post-MI periods in predicting AR. Regression analysis showed that a low sCD163/TWEAK ratio at the first day post-MI had an independent association with AR, regardless of infarct size. A larger infarct size can cause an immune system reaction, such as a cytokine storm, causing more damage to the heart [3]. In the AR and non-AR groups, the infarct size showed no characteristic healing differences, while there were positive correlations between infarct size and sCD163 and TWEAK concentrations. Contrary to this relationship, a negative correlation was found between infarct size and the sCD163/TWEAK ratio. However, the degree of correlation was higher in the AR group. This may be related to the severity of the inflammatory response [1]. We can explain this hypothesis with higher CRP in AR patients. A higher TWEAK release and lower sCD163/TWEAK ratio can be observed, depending on the increased inflammatory response. Therefore, infarct size may indirectly contribute to the development of AR through the inflammatory response.

Observing the prevention of AR after post-MI administration of TWEAK inhibitors is necessary to clearly verify that TWEAK causes AR during the post-MI period. In addition, local cardiomyocyte concentrations of TWEAK should also be measured to determine whether TWEAK is effective in cardiac remodeling by its action on cardiomyocytes. Although this measurement is not possible in human models, TWEAK upregulation is reported in cardiomyocytes of animal models [23].

Limitations

The main limitation of our study was the low number of patients. Secondly limitation was that the determined TWEAK concentration was a systemically measured variable. Thirdly, we could not include a healthy control group in this study. Finally, other cytokines or microRNA interacting with the TWEAK were not investigated in this study.

Conclusions

Although the important role of TWEAK in the pathogenesis of AR after MI is known, it appears to be a promising biomarker when combined with sCD163 in the early phase, post-MI. We found that the sCD163/TWEAK ratio at the first day post-MI was lower in the AR group, while no difference existed between the groups at 14 days post-MI. This change demonstrated a high diagnostic performance in predicting AR. Therefore, the sCD163/TWEAK ratio may be an important biomarker for predicting AR in the early phase, post-MI.

Ethical approval

The study was performed in accordance with the Declaration of Helsinki, and approved by the Faculty Of Medicine Non-Drug Clinical Research Ethics Committee of the Ankara Yildirim Beyazit University, on 24 June 2013, under Decision No. 2013/106. Written informed consent was obtained from all patients.

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No conflict of interest is reported.

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