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EVALUATION OF THE RELATIONSHIP BETWEEN ANTI-INFLAMMATORY CYTOKINES AND ADVERSE CARDIAC REMODELING AFTER MYOCARDIAL INFARCTION

| | |
|-----------------------------|---|
| <i>Aim</i> | To clarify the role of interleukin (IL) – 10 and members of its subfamily (IL-19 and IL-26) in cardiac remodeling during the post-myocardial infarction (MI) period. |
| <i>Material and methods</i> | A total of 45 patients with ST-segment elevation MI were enrolled. Serum cytokine concentrations were measured at the first day and 14 days post-MI. Left ventricular (LV) reverse remodeling (RR) was defined as the reduction of LV end-diastolic volume or LV end-systolic volume by $\geq 12\%$ in cardiac magnetic resonance images at 6-mo follow-up. A 12% increase was defined as adverse remodeling (AR). |
| <i>Results</i> | The post-MI first-day median IL-10 (9.7 pg/ml vs. 17.6 pg/ml, $p<0.001$), median IL-19 (28.7 pg/ml vs. 36.9 pg/ml, $p<0.001$), and median IL-26 (47.8 pg/ml vs. 90.7 pg/ml, $p<0.001$) were lower in the RR group compared to the AR group. There was a significant decrease in the concentration of anti-inflammatory cytokines in the AR group from the first to the 14 days post-MI. However, no significant change was observed in the RR group. Regression analysis revealed that a low IL-10 concentration on the post-MI first day was related to RR (OR=0.76, $p=0.035$). A 1% increase in change of IL-10 concentration increased the probability of RR by 1.07 times. |
| <i>Conclusion</i> | The concentrations of cytokines were higher in the AR group, but this elevation was not sustained and significantly decreased for the 14 days post-MI. In the RR group, the concentrations of cytokines did not change and stable for the 14 days post-MI. As a reflection of this findings, stable IL-10 concentration may play a role the improvement of cardiac functions. |
| <i>Keywords</i> | Adverse remodeling; IL-10; IL-19; IL-26; myocardial infarction; reverse remodeling |
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Introduction

Cardiac remodeling occurs as a result of inflammatory/anti-inflammatory homeostasis that develops after acute myocardial infarction (MI). While an excessive inflammatory response induces adverse remodeling (AR), moderate inflammatory and strong anti-inflammatory responses can cause reverse remodeling (RR) [1]. Pro-inflammatory cytokines, such as tumor necrosis factor (TNF) – α , interleukin (IL) – 1β , and IL-6, which increase in the early post-MI period, are known to cause apoptosis, collagen production, matrix metalloproteinase (MMP) activation, fibrosis, and ventricular dilation that, in turn, cause ventricular failure [1–3]. It is thought that an increased anti-inflammatory response during this

process would suppress inflammation and improve cardiac function [4].

One of the cytokines thought to play a major role in the anti-inflammatory balance in the post-MI period is IL-10 [5]. It is a powerful anti-inflammatory cytokine, as well as a cytokine synthesis inhibitor in humans [6]. In the post-MI period, IL-10 inhibits lipopolysaccharide-induced production of pro-inflammatory cytokines, such as TNF- α , IL-1, and IL-6 [7, 8]. IL-10 also acts as an antioxidant. It inhibits the production of reactive oxygen species by TNF- α in cardiac myocytes [9]. Experimental studies in mice with IL-10 deficiency have confirmed that an increase in neutrophil infiltration increases myocardial infarct size [10].

IL-19, one of the IL-10 superfamily cytokines, was first discovered in the 2000s [11]. It is mainly secreted by lymphocytes, macrophages, and monocytes. It is a multifunctional cytokine that is also secreted in small amounts by non-immune cells, such as smooth muscle cells and endothelial cells [12]. IL-19 binds to IL-20R1/IL-20R2 on target cells [13, 14]. By activating the JAK/STAT pathway, it participates in the progression of many systemic diseases including ischemia/reperfusion injury of the brain and kidneys, psoriasis, and angiogenesis in diabetes. Some recent studies have also focused on the cardioprotective effect of IL-19 [15, 16].

IL-26 is another cytokine of the IL-10 superfamily. IL-26 is produced by macrophages, natural killer cells, and T helper (Th) – 1 and Th-17 cells [17]. Recent studies have demonstrated that IL-26 plays a role in the etiopathogenesis of autoimmune diseases, such as colitis, rheumatoid arthritis, and psoriasis [18]. We have not found any study that examined the role of IL-26 in acute coronary syndrome and cardiac remodeling.

In this study, we aimed to examine the role of IL-10 and members of its superfamily, IL-19 and IL-26, in cardiac remodeling during the post-MI period.

Material and methods

Study population and design

This study was planned as a multi-center, prospective study from June 2015 through June 2016. The study was designed in accordance with the Helsinki Declaration and with good clinical practices guidelines. All participants signed informed, voluntary consent forms. Approval was obtained from the local ethics committee. Assuming an alpha of 0.05, a power of 0.80, and with an 20% estimated adverse remodeling (AR) rate, in agreement with previous reports, the estimated sample size was at least 40 patients.

Two hundred eighteen ST-segment elevation MI (STEMI) patients above the age of 18 who presented within the first 12 hrs after the onset of chest pain ongoing for more than 30 min with >0.1 mV ST-segment elevation in two or more related leads, and who underwent primary percutaneous coronary intervention (PCI) were evaluated in the study. The definition of STEMI was according to the third universal definition of myocardial infarction (MI) [19] and was managed according to the latest European Society of Cardiology guidelines [20]. 167 patients were excluded from the study (see exclusion criteria below). In 6 of the remaining 51 patients, no change in volumes or less than 12% change was observed at the 6-mo follow-up examination, and these patients were also excluded. The remaining 45 patients were included in the study

Exclusion criteria:

- 1) in cardiogenic shock or in need of an intra-aortic balloon pump;
- 2) an estimated glomerular filtration rate (eGFR) ≤ 30 ml/min/1.73 m²;
- 3) Killip class ≥ 3 ;
- 4) a history of silent ischemia or infarct;
- 5) right coronary artery occlusion;
- 6) any kind of systemic inflammatory disease;
- 7) autoimmune disease;
- 8) a history of chronic corticosteroid or anti-inflammatory drugs;
- 9) pregnancy or delivery within the last 90 days or breastfeeding;
- 10) emergency or elective coronary artery bypass grafting planned after the angiography;
- 11) patients who had myocardial re-infarction during follow up.

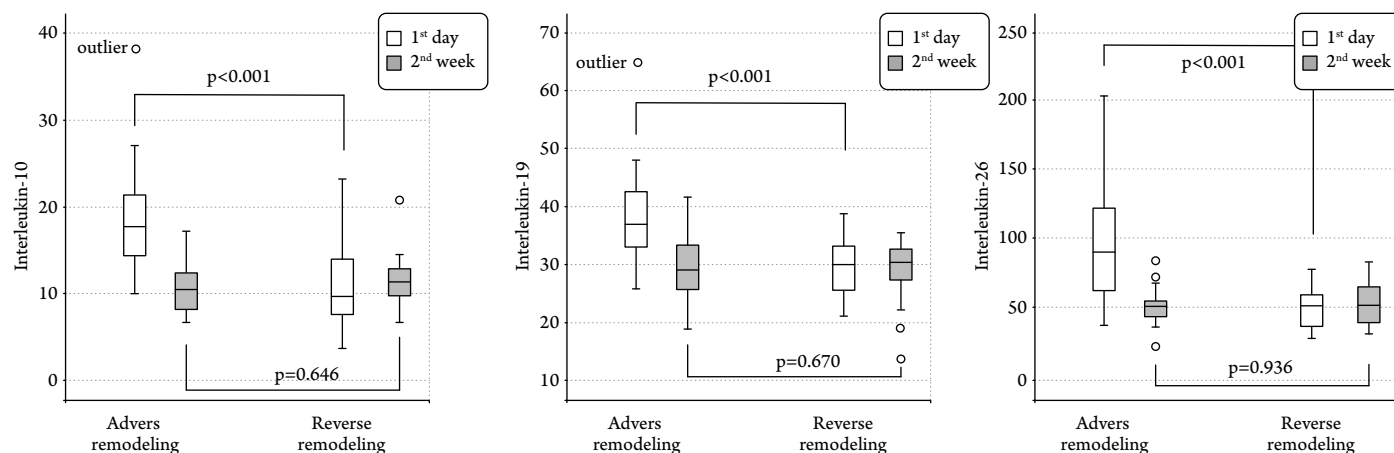
Left ventricular (LV) RR was defined as the reduction of LV end-diastolic volume (LVEDV) or LV end-systolic volume (LVESV) by $\geq 12\%$ in cardiac magnetic resonance (CMR) images at 6-mo follow-up, and a 12% increase was defined as AR [21, 22]. Clinical, demographic, laboratory, and radiological findings were recorded in a timely manner in the patients' files during follow-up.

Biochemical analyses

Venous blood samples were taken for hemoglobin, cardiac troponin I, C-reactive protein (CRP), and a lipid panel at the time of the patient's admission. Cytokine markers were assessed at the first day and 14 days postMI. Blood samples were centrifuged at 1500 rpm for 10 min and were stored at -80°C . Analyses were performed after all samples were collected and done in the same laboratory by the same technician in a single session and with the same device. Total cholesterol was determined by the homogeneous enzymatic colorimetric method in a Hitachi Modular P800 autoanalyzer (Roche Diagnostics Corp., Indianapolis, IN, USA). Low density lipoprotein (LDL) was calculated according to Friedewald method [23].

Cytokine quantification was run in duplicate. Serum samples were thawed on ice and concentrations of IL were analyzed according to the manufacturer's instructions for the bead-based multiplex immunoassay system (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 of analytes was calculated using the Bio-Plex Manager v5.0 software package (Bio-Rad). For all statistical analyses, values below the detection limit of the assay were replaced with the

Figure 1. Concentrations of cytokines in cardiac remodeling groups at first day vs 14 days post-MI



minimal detectable value for the analyte. The coefficient of variation (CV%) was <10%.

CMR imaging

All CMR studies were performed with a 3 Tesla scanner (Magnetom Skyra, Siemens Medical Systems, Erlangen, Germany) at 14 days and six mos post-MI. The applied imaging protocol was published previously in detail [24]. The CMR imaging protocol included acquisition of one 4-chamber view, cine short-axis sections (6-mm slice thickness at 10-mm intervals), and one 2-chamber view. The indices of LV systolic function were assessed by using the retrospective electrocardiogram-gated, turbo-fast low angle-shot (turbo-FLASH) sequence. Imaging parameters were as follows: echo time (TE) 1.42 ms, repetition time (TR) 39 ms, flip angle 57°, voxel size 1.67 × 1.67 × 6 mm. Cardiac function and volumes were measured using Syngo via imaging software (Siemens). LVEDV and LVESV were calculated with short-axis based planimetry from the basal to the apical level. LV stroke volume was calculated as LVEDV minus LVESV, and LV ejection fraction (LVEF) was calculated as: $EF = [(LVEDV - LVESV) / LVEDV] \times 100$.

Statistical analysis

Statistical analyses were performed using SPSS 20 for Windows (IBM Corp., Armonk, NY, USA). The normality data distributions was evaluated by the Shapiro-Wilk test. Numeric variables with or without normal distribution were plotted as mean ± standard deviation or as median (interquartile range (IQR): 25th -75th percentile), respectively. Categorical variables are indicated as numeric and percentage values. Student-T test or Mann-Whitney U test were used for comparison of numeric variables between the two groups according to the distribution normality. Chi-square with Yates correction and Fischer's exact tests were used for comparison of categorical data. A mixed model for repeated measures analysis was

performed for comparison of cytokine concentrations in the post-MI period and during follow-up according to the remodeling groups. Logistic regression analysis was used to identify independent predictors of reverse remodeling (RR). Values of $p < 0.05$ (*) were considered statistically significant. Changes in CMR variables and cytokine concentrations in the post-MI period are shown by Δ . The relationship between cytokine concentrations and CMR parameters was examined by Spearman correlation analysis.

Results

Detailed demographic, laboratory, and clinical findings at the time of admission of the study population are shown in Table 1. The study population consisted of 5 women and 40 men (mean age: 55.6 ± 7.4 yrs). 20 patients (44.4%) had hypertension. RR was detected in 26 patients at the end of 6 mos. There was no significant differences in demographic, laboratory, and clinical findings among AR and RR groups.

Cardiac MRI findings of the RR and AR groups did not show significant differences at the 14 days post-MI. Mean LVEF was higher (50.5 ± 8.0% vs. 44.3 ± 10.4%, $p = 0.030$) and mean LVEDV (144.7 ± 31.0 ml vs. 186.1 ± 33.1 ml, $p < 0.001$) and median LVESV (74.5 ml vs. 107 ml, $p = 0.012$) were lower in the RR group compared to the AR group after 6 mos. At the 6 mos post-MI, there was a significant worsening of LV volume and functions in AR group compared to RR group. (Table 2).

At the first day post-MI, median IL-10 (9.7 pg/ml vs. 17.6 pg/ml, $p < 0.001$), median IL-19 (28.7 pg/ml vs. 36.9 pg/ml, $p < 0.001$), and median IL-26 (47.8 pg/ml vs. 90.7 pg/ml, $p < 0.001$) were lower in the RR group compared the AR group. At the 14 days post-MI, cytokine concentrations were not significantly different between the groups (Figure 1). In the RR group, there were no significant changes in concentrations of the IL family members in the 14 days compared to the first day post-MI (Table 3).

Table 1. Demographic, laboratory, and clinical findings of the study population

| Variables | All population | Remodeling | | p |
|----------------------------------|----------------|-------------|-------------|--------|
| | | RR | AR | |
| | n=45 | n=26 | n=19 | |
| Demographic findings | | | | |
| Age, yrs | 55.6±7.4 | 56.4±8.0 | 54.5±6.4 | 0.409 |
| Gender | | | | |
| Female | 5 (11.1) | 2 (7.7) | 3 (15.8) | 0.709 |
| Male | 40 (88.9) | 24 (92.3) | 16 (84.2) | |
| Smoking | 21 (46.7) | 10 (38.5) | 11 (57.9) | 0.237 |
| Hypertension | 20 (44.4) | 11 (42.3) | 9 (47.4) | 0.770 |
| Diabetes mellitus, n (%) | 11 (24.4) | 6 (23.1) | 5 (26.3) | 0.807 |
| SBP, mm Hg | 128±19 | 127±16 | 129±20 | 0.711 |
| DBP, mm Hg | 75±11 | 74±10 | 75±14 | 0.780 |
| HR, beat per minute | 80±10 | 78±9 | 82±11 | 0.187 |
| Door-to-balloon time, min | 44.2±12.5 | 43.5±12.3 | 45.8±12.7 | 0.544 |
| Symptom-to-balloon time, min | 314.5±90.1 | 310.5±88.6 | 320.5±92.5 | 0.715 |
| Laboratory findings | | | | |
| cTn-I, ng/L | 22.8 (20.3) | 21.1 (17.9) | 24.2 (22.2) | 0.696 |
| WBC, ×10 ⁹ /l | 11.5±3.5 | 11.6±3.9 | 11.3±2.9 | 0.754 |
| Neutrophils, ×10 ⁹ /l | 70.6±11.6 | 71.2±12.2 | 69.8±10.9 | 0.694 |
| Lymphocytes, ×10 ⁹ /l | 16.9 (13.4) | 16.5 (14.6) | 19.9 (15.7) | 0.512 |
| Monocytes, ×10 ⁹ /l | 7.1 (4.7) | 6.8 (3.6) | 7.7 (4.1) | 0.194 |
| Platelets, ×10 ⁹ /l | 228.1±58.5 | 229.8±60.9 | 225.7±56.5 | 0.817 |
| Total cholesterol, mg/dl | 194.0±38.4 | 192.6±35.1 | 195.9±43.4 | 0.777 |
| LDL, mg/dl | 131 (30) | 136 (41) | 130 (30) | 0.927 |
| HDL, mg/dl | 37.2±8.2 | 37.8±10.1 | 36.4±4.7 | 0.555 |
| Triglycerides, mg/dl | 146 (90) | 132.5 (110) | 158 (85) | 0.662 |
| Creatinine, mg/dl | 1.0±0.2 | 1.0±0.2 | 1.0±0.3 | 0.779 |
| hs-CRP, mg/l | 16 (15.8) | 12.5 (14) | 20 (17.2) | 0.013* |
| Discharge therapy | | | | |
| ACE/ARB | 38 (84.4) | 22 (84.6) | 16 (84.2) | 0.999 |
| Beta blockers | 33 (73.3) | 19 (73.1) | 14 (73.7) | 0.999 |
| Statins, n (%) | 42 (93.3) | 24 (92.3) | 18 (94.7) | 0.999 |

Data are mean±standard deviation, median (IQR), or number (%). cTn-I, cardiac troponin I; WBCs, white blood cells; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; RR, reverse remodeling; AR, adverse remodeling; *, considered statistically significant (p<0.05.).

Table 2. Results of cardiac magnetic resonance imaging

| Variables | 14 days post-MI | | | 6th month post-MI | | | Δp |
|-------------------|-----------------|------------|-------|-------------------|------------|---------|---------|
| | Remodeling | | p | Remodeling | | p | |
| | RR | AR | | RR | AR | | |
| | n=26 | n=19 | | n=26 | n=19 | | |
| LVEF, % | 45.8±10 | 48.5±10.5 | 0.377 | 50.5±8.0 | 44.3±10.4 | 0.030* | <0.001* |
| LVEDV, ml | 166.2±35.9 | 158.8±28.3 | 0.458 | 144.7±31.0 | 186.1±33.1 | <0.001* | <0.001* |
| LVESV, ml | 93.5 (75) | 97 (72) | 0.671 | 74.5 (68) | 107 (84) | 0.012* | <0.001* |
| Stroke volume, ml | 74.7±8.6 | 76.2±16.4 | 0.692 | 75.5±11.5 | 73.3±16.9 | 0.605 | 0.019* |
| CO, ml/min | 4.5±0.8 | 5.1±1.2 | 0.053 | 4.9±0.9 | 4.8±1.5 | 0.789 | 0.014* |
| CI, ml/min/m² | 2.5±0.4 | 2.7±0.5 | 0.126 | 2.7±0.5 | 2.6±0.5 | 0.442 | 0.012* |

Data are mean±standard deviation or median (IQR). CI, cardiac index; CO, cardiac output; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; RR, reverse remodeling; AR, adverse remodeling. *, considered statistically significant (p<0.05.).




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*Валсартан, олмесартан. **Статистически значимое превосходство в снижении клинического систолического АД vs. валсартан 320 мг и олмесартан 40 мг^{3,4}.

Информация для специалистов здравоохранения. 1. Инструкция по применению лекарственного препарата для медицинского применения Эдарби®, таблетки 20 мг, 40 мг, 80 мг. Рег. уд. ЛП-002359 от 03.02.2014. 2. Bakris G., et al. J. Clin. Hypertens. (Greenwich). 2011; 13(2): 81–8. 3. Sica D., et al. J. Clin. Hypertension (Greenwich). 2011; 13: 467–472. 4. White W., et al. Hypertension. 2011; 57(3): 413–20.

Сокращенная информация по применению

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Полный перечень побочных эффектов содержится в инструкции по медицинскому применению.

С осторожностью: тяжелая хроническая сердечная недостаточность (IV функциональный класс по классификации NYHA); почечная недостаточность тяжелой степени (клиренс креатинина < 30 мл/мин); двусторонний стеноз почечных артерий и стеноз артерии единственной функционирующей почки; ишемическая кардиомиопатия; ишемические цереброваскулярные заболевания; состояние после трансплантации почки; состояние,

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Table 3. Concentrations of cytokines among RR and AR groups

| Variables | Remodeling | First day post-MI | | 14 days post-MI | | P _{time} | Δp |
|--------------|------------|-------------------|---------|-----------------|-------|-------------------|---------|
| | | Median (IQR) | p | Median (IQR) | p | | |
| IL-10, pg/ml | RR = 26 | 9.7 (6.3) | <0.001* | 11.3 (3.2) | 0.646 | 0.611 | <0.001* |
| | AR = 19 | 17.6 (8.1) | | 10.4 (4.7) | | <0.001* | |
| IL-19, pg/ml | RR = 26 | 28.7 (7.4) | <0.001* | 30.3 (4.9) | 0.670 | 0.574 | 0.002* |
| | AR = 19 | 36.9 (11.7) | | 29.1 (7.7) | | 0.002* | |
| IL-26, pg/ml | RR = 26 | 47.8 (22.7) | <0.001* | 51.1 (24.8) | 0.936 | 0.600 | <0.001* |
| | AR = 19 | 90.7 (62.3) | | 50.9 (12) | | <0.001* | |

Data are median (IQR). p_{time}, 1st day vs 2nd week within remodeling groups; Δp, 1st day vs 14 days post-MI between the remodeling groups (RR vs AR); IL, interleukin; RR, reverse remodeling; AR, adverse remodeling; *, considered statistically significant (p<0.05.).

Multivariable regression analysis including IL-10, IL-19, and IL-26 cytokines on the first day post-MI (Model I) revealed IL-10 as an independent predictor of RR. According to this analysis, an increase of 1 pg/ml in the concentration of IL-10 would decrease the odds of RR by 1.32-fold (OR=0.76, p=0.035). In addition, the regression model in which changes in post-MI cytokine concentrations (Model II) were included showed that a 1% increase in ΔIL-10 increased the odds of RR by 1.07-fold (OR=1.07, p=0.007). Besides, the model II exhibited a higher goodness of fit compared to Model I (Model I Nagelkerke R²: 0.43 vs Model II Nagelkerke R²: 0.54) (Table 4).

There was a positive correlation between IL-10 concentration and LVEF levels, and a negative correlation between LVEDV in both RR and AR groups (Table 5).

Discussion

In this study, at the first day post-MI, the concentration of anti-inflammatory cytokines was higher in the AR group than in the RR group. There was a significant decrease in the concentration of anti-inflammatory cytokines at the 14 days compared to first day post-MI in the AR group. However, no significant decrease was observed in the RR

group. Multivariable regression analysis revealed that an increase of IL-10 on the first day post-MI was related to reduced the odds of RR. On the other hand, multivariable regression analysis showed that a 1% increase in the change of IL-10 concentration increased the odds of RR by 1.07-fold. The regression model in which changes in post-MI cytokine concentrations exhibited a higher goodness of fit.

In acute STEMI, the process of cardiac repair is molded by the degree of inflammation, oxidative stress, and hemodynamic changes after ischemia. The lower are these risk factors and the higher are the concentrations of antioxidant molecules and anti-inflammatory markers, the higher will be the probability of developing RR. In comparison, the likelihood of developing AR will be greater if there is an excessive inflammatory response and increased reactive oxidant radicals in the presence of a weak antioxidant balance and a weak anti-inflammatory response [25]. A study by Meng et al. [26] assessed whether amniotic mesenchymal stem cells (AMM/I) regulated by the IL-10 gene contributed to LV function and remodeling after acute MI. They found that AMM/I produced by gene regulation suppresses severe pro-inflammatory responses by its effects on post-

Table 4. Regression analysis of the effects of cytokines on reverse remodeling

| Follow-up | Cytokines | Univariable | | | Multivariable | | |
|-----------------------|-----------|-------------|--------------|--------|---|--------------|--------|
| | | OR | 95% CI | p | OR | 95% CI | p |
| | | | Lower; upper | | | Lower; upper | |
| Model I (First day) | IL-10 | 0.69 | 0.56; 0.86 | 0.001* | 0.76 | 0.59; 0.98 | 0.035* |
| | IL-19 | 0.79 | 0.68; 0.92 | 0.003* | - | - | - |
| | IL-26 | 0.91 | 0.87; 0.97 | 0.002* | - | - | - |
| | | | | | Nagelkerke R ² =0.43; p<0.001* | | |
| Model II (Change (Δ)) | IL-10 | 1.06 | 1.03; 1.10 | 0.001* | 1.07 | 1.02; 1.12 | 0.007* |
| | IL-19 | 1.05 | 1.01; 1.08 | 0.013* | - | - | - |
| | IL-26 | 1.07 | 1.03; 1.12 | 0.001* | - | - | - |
| | | | | | Nagelkerke R ² =0.54; p<0.001* | | |

Reference group: adverse remodeling. All analysis were adjusted for age, sex, and smoking, comorbidities, symptom to balloon time, troponin concentrations, hs-CRP and cardiac output. Model I included cytokine concentrations measured on day 1 post-MI. Model II included changes in cytokine concentrations from day 1 to day 14 post-MI. IL, interleukin; OR, odds ratio; CI, confidence interval;

*, considered statistically significant (p<0.05).

Table 5. Relationship between IL-10 superfamily concentrations and CMR measurements

| Groups | Cytokines | 14 days post-MI | | | | | | Change (Δ) | | | | | |
|--------|---------------------|-----------------|-------|--------|-------|--------|-------|---------------------|--------|--------|--------|--------|--------|
| | | LVEF | | LVEDV | | LVESV | | LVEF | | LVEDV | | LVESV | |
| | | r | p | r | p | r | p | r | p | r | p | r | p |
| AR | First day post-MI | | | | | | | | | | | | |
| | IL-10 | -0.221 | 0.420 | -0.009 | 0.970 | 0.061 | 0.803 | 0.485 | 0.035 | -0.512 | 0.027* | -0.421 | 0.049* |
| | IL-19 | -0.123 | 0.616 | 0.080 | 0.746 | -0.129 | 0.599 | 0.415 | 0.042* | -0.447 | 0.038* | -0.342 | 0.139 |
| | IL-26 | -0.052 | 0.833 | -0.038 | 0.878 | -0.043 | 0.861 | 0.417 | 0.040* | -0.435 | 0.045* | -0.344 | 0.142 |
| | 14 days post-MI | | | | | | | | | | | | |
| | IL-10 | -0.158 | 0.517 | -0.122 | 0.618 | 0.013 | 0.959 | 0.046 | 0.852 | -0.023 | 0.926 | 0.081 | 0.742 |
| | IL-19 | -0.073 | 0.765 | -0.102 | 0.679 | 0.013 | 0.957 | 0.209 | 0.290 | -0.259 | 0.284 | -0.119 | 0.627 |
| | IL-26 | -0.208 | 0.440 | 0.018 | 0.940 | 0.229 | 0.469 | 0.267 | 0.269 | -0.117 | 0.634 | 0.146 | 0.551 |
| | Change (Δ) | | | | | | | | | | | | |
| | IL-10 | 0.143 | 0.559 | -0.116 | 0.637 | -0.039 | 0.872 | 0.441 | 0.047* | -0.558 | 0.015* | -0.394 | 0.122 |
| | IL-19 | 0.039 | 0.874 | -0.089 | 0.718 | 0.100 | 0.684 | 0.382 | 0.117 | -0.440 | 0.040* | -0.314 | 0.167 |
| | IL-26 | -0.132 | 0.591 | 0.051 | 0.836 | 0.205 | 0.399 | 0.422 | 0.048* | -0.437 | 0.045* | -0.321 | 0.146 |
| RR | First day post-MI | | | | | | | | | | | | |
| | IL-10 | -0.108 | 0.600 | 0.079 | 0.701 | 0.044 | 0.830 | 0.487 | 0.030* | -0.509 | 0.019* | -0.398 | 0.050* |
| | IL-19 | -0.100 | 0.626 | 0.025 | 0.902 | 0.023 | 0.911 | 0.433 | 0.040* | -0.486 | 0.025* | -0.340 | 0.155 |
| | IL-26 | 0.193 | 0.346 | -0.113 | 0.581 | -0.187 | 0.359 | 0.426 | 0.046* | -0.459 | 0.037* | -0.345 | 0.138 |
| | 14 days post-MI | | | | | | | | | | | | |
| | IL-10 | -0.246 | 0.184 | 0.299 | 0.137 | 0.292 | 0.148 | 0.275 | 0.175 | -0.264 | 0.318 | -0.207 | 0.389 |
| | IL-19 | -0.250 | 0.218 | 0.247 | 0.223 | 0.255 | 0.209 | 0.242 | 0.233 | -0.189 | 0.667 | -0.171 | 0.630 |
| | IL-26 | -0.283 | 0.161 | 0.248 | 0.181 | 0.290 | 0.151 | 0.160 | 0.436 | -0.288 | 0.303 | -0.156 | 0.448 |
| | Change (Δ) | | | | | | | | | | | | |
| | IL-10 | -0.154 | 0.452 | 0.125 | 0.543 | 0.183 | 0.372 | 0.406 | 0.050* | -0.495 | 0.019* | -0.322 | 0.114 |
| | IL-19 | -0.069 | 0.739 | 0.160 | 0.435 | 0.164 | 0.422 | 0.359 | 0.107 | -0.402 | 0.042* | -0.346 | 0.107 |
| | IL-26 | -0.283 | 0.133 | 0.290 | 0.149 | 0.285 | 0.164 | 0.346 | 0.119 | -0.418 | 0.039* | -0.353 | 0.098 |

IL, interleukin; RR, reverse remodeling; AR, adverse remodeling; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume.

MI angiogenesis and prevents AR, and that AMM/I has a cardioprotective effect. During the post-MI period of 30 patients with acute coronary syndrome, a positive correlation between IL-8 concentration and LV systolic volume was found. IL-10 concentration correlated negatively with LV end diastolic diameter and with left atrial volume [25]. Falcao et al. [27] determined that IL-10 concentrations produced using whole blood cultures in the 72nd-hr post-MI were negatively correlated with LVEDV and LVESV. A study in mice demonstrated that endogenous IL-10 released from leukocytes during acute MI exerted a cardioprotective action by associated with of endothelial progenitor cells in bone marrow [28].

In a study in rats, the animals were given recombinant IL-10 treatment during acute MI [29]. This treatment significantly contributed to cardiac RR in the post-MI period in rats. In a Korean study [30], IL-10 knockout mice and wild-type mice were given angiotensin II infusions for a week. After this procedure, cardiac function was significantly decreased in the IL-10 knockout mice compared to the wild-type mice. The researchers suggested that IL-10 plays a protective role against angiotensin II-induced cardiac remodeling.

Based on the above findings, it can be postulated that IL-10 decreased the progression to AR by reducing excessive inflammatory responses in the post-MI period. Correlation analysis showed that increased IL-10 concentration was associated with increased LVEF levels and decreased LVEDV levels in both the RR and AR groups. This suggests that increases in IL-10 concentrations in the post-MI period are cardioprotective. Meng et al. [26] detected of IL-10 concentration in heart tissues after 3 days in AMM/I mice. They found that the not significant improvement in LV function at 2 weeks, but significant improvement in EF at 4 weeks. Falcao et al. [27] measured IL-10 concentrations 72 hours after the onset of symptoms, and LV volumes 24–96 hours and 10–14 weeks after admission. They found that the a negative correlation between IL-10 concentration and changes in LV volume indices. The results of the correlation analysis in our study showed that there was no correlation between the cytokine concentrations at the first day post-MI and LVEF and LV volumes at the 14 days pos-MI, which were in line with the literature. These findings suggest that the cardioprotective effect of IL-10 may be in the long run.

On the other hand, in our study and similar to the studies cited above, CRP levels were higher in the AR group than

in the RR group on the first day post-MI. At the same time, the IL-10 concentration measured was higher in the AR group compared to the RR group. This suggests that the excessive of IL-10 concentration measured in the AR group may be associated with an excessive inflammatory response. The presence of excessively increased IL-10 concentration on the first day post-MI in the AR group explain the association of high IL-10 concentration with a reduced the odds of RR in the model I regression analysis. Besides, there was a significant decrease in the concentration of IL-10 at the 14 days compared to first day post-MI in the AR group. IL-10 concentration did not change in the RR group. As a reflection of this findings, model II regression analysis revealed that the increased concentration of Δ IL-10 in the post-MI periods was increased the odds of RR.

A main finding of recent studies has been that IL-19 has a protective effect on cardiovascular structures due to its anti-inflammatory actions [29, 30]. In a study conducted in mice by Ellison et al. [15], IL-19 treatment was shown to inhibit atherosclerosis by alleviating inflammation in bone marrow-derived macrophages, endothelial cells, and vascular smooth muscle cells. In a Chinese study [31], exogenous IL-19 was given to mice that had undergone MI. IL-19 decreased MI and apoptosis by increasing heme oxygenase-1 activity and by decreasing malondialdehyde formation. As a result, it appeared that IL-19 would decrease acute ischemic damage and increase survival in mice. In our study, the IL-19 concentration was higher in the AR group compared to the RR group on first day post-MI. While there was a significant decrease in the IL-19 concentration in the AR group from the first day to the 14 days post-MI, in the RR group, although not significant, there was an partial increase in the IL-19 concentration from the first day to the 14 days post-MI. These findings suggest that IL-19 has a cardioprotective effect. Although this effect is related to the anti-inflammatory actions of IL-19, it may also be associated with IL-19-induced increase in the concentration of IL-10, a cardioprotective cytokine [32].

We have not found any studies on the role of IL-26, a recently discovered member of the IL-10 subfamily, in cardiac remodeling. However, its roles in the pathogenesis of autoimmune diseases, rheumatoid arthritis, psoriasis, and colitis have been studied. In our study, the IL-26 concentration was significantly higher in the AR group on

the first day post-MI, and a significant decrease in IL-26 concentration was observed in this group at the 14 days post-MI. In the RR group, although not significant, an partial increase was observed in the concentration of IL-26 from the first day to the 14 days post-MI. In light of these findings, we can postulate that the persistently high concentration of IL-26, an anti-inflammatory cytokine, for 14 days post-MI in the RR group was responsible for cardioprotective effect.

The main limitations of this study are its cross-sectional design and the small size of the study population. In this study, we evaluated only the relationships between systemic concentrations of anti-inflammatory cytokines and cardiac remodeling. Evaluation of anti-inflammatory cytokines in cardiac tissue and their relationship with pathological findings in the post-MI period would have made this study stronger.

Conclusion

Cardiac remodeling occurs as a result of inflammatory/anti-inflammatory homeostasis that develops after STEMI. We found that anti-inflammatory cytokine concentrations were higher in the AR group in the post-MI period and this elevation was not sustained and significantly decreased for the 14 days post-MI. In the RR group, we determined that the rise of anti-inflammatory cytokine concentrations in the post-MI period was permanent for the 14 days post-MI. As a reflection of this findings, stable IL-10 concentration may play a role the improvement of cardiac functions.

Authors' Contribution

FE, EK and EN conceived and designed the work. GK, contributed to data acquisition. OK and OY, analyzed, and interpreted the data. FE drafted the manuscript. EN and EK revised the manuscript critically for important intellectual content.

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