PCSK9 Inhibitor Induces a Transient Decrease in Neutrophil-Lymphocyte Ratio and Monocyte-Lymphocyte Ratio in Homozygous/Compound Heterozygous Familial Hypercholesterolemia Patients

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Research Article

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Abstract

Background: Homozygous/compound heterozygous familial hypercholesterolemia (HoFH/cHeFH) is characterized by extremely elevated low-density lipoprotein-cholesterol (LDL-C) levels that have been reported to contribute to a long-term chronic systemic inflammation. The aims of this study are to describe the inflammatory profile of HoFH/cHeFH patients and explore the effect of PCSK9 inhibitor (PCSK9i) on a series of inflammatory biomarkers, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-HDL ratio (MHR), monocyte-lymphocyte ratio (MLR) and mean platelet volume-lymphocyte ratio (MPVLR).

Methods: In this prospective cohort study, 21 definitive HoFH/cHeFH on high-intensity statins plus ezetimibe were placed on subcutaneous injections of PCSK9i 450mg every 4 weeks (Q4W). The biochemical parameters and inflammatory profile were analyzed at the day before PCSK9i therapy, 3 months and 6 months after PCSK9i therapy.

Results: We found that HoFH/cHeFH on maximum tolerated statin dose plus ezetimibe displayed an elevated lipid and disturbed blood biomarker profile. After 3 months of add-on PCSK9i therapy, a significant reduction of LDL-C was observed. Meanwhile, percentage and count of neutrophils, monocyte counts, MPV, as well as two inflammatory biomarkers, NLR and MLR were reduced. However, at 6-month PCSK9i treatment, NLR and MLR returned to pre-PCSK9i treatment levels.

Conclusions: PCSK9i induces a transient decrease in NLR and MLR in HoFH/cHeFH patients. Our results add evidence in evaluating the effects of PCSK9i on systemic inflammation.

Background

Familial hypercholesterolemia (FH) is an autosomal dominant hereditary disease that is characterized by elevated levels of total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) levels[1], premature atherosclerosis (AS) and cardiovascular diseases (CVD). The most frequent reported gene mutated in FH is LDL-receptor (LDLR), accounting for 85-90% of reported cases. In addition, mutation in apolipoprotein B (APOB), proprotein convertase subtilisin/kexin-9 (PCSK9), low-density lipoprotein receptor adaptor protein 1(LDLRAP1) have also been described in causing FH[2]. In the general population, the prevalence of heterozygous FH (HeFH) patients who carry a mutation in one of the alleles is about 1 in 300[3,4], while homozygous/compound heterozygous FH (HoFH/cHeFH) patients in which both of their alleles harbor mutations may affect 1 in 160,000-300,000 individuals[5], and usually have higher LDL-C levels and poorer clinical prognosis than HeFH[5].

Of note, in addition to causing abnormally high blood lipid levels, hypercholesterolemia induces chronic systemic and vascular inflammation[6,7,8,9]. A number of immunocytes and blood components such as monocytes[10], macrophages[11], dendritic cells[12], lymphocytes[13], neutrophils[14], platelets[15] and complement system[16], have been reported to contribute to the pro-inflammatory environment in AS,

promoting the development of atherogenesis, plaque destabilization and plaque erosion. A series of blood cellular component-related parameters, such as neutrophil-lymphocyte ratio (NLR)[17,18], platelet-lymphocyte ratio (PLR)[19,20], monocyte-HDL ratio (MHR)[21,22], monocyte-lymphocyte ratio (MLR)[23,24] and MPV-lymphocyte ratio (MPVLR)[25] have been used to illustrate systemic inflammation status and evaluate the risk of future CVD events. The treatment of hypercholesterolemia patients should focus not only on lipid lowering but also on reducing chronic inflammation[26,27].

As the first-line pharmacological treatment for dyslipidemia, statins can significantly reduce the level of LDL-C and the risk of cardiovascular events[28]. However, the majority of FH patients[29], especially HoFH patients[30], could not achieve optimal LDL-C reduction even with the maximum tolerated doses of statins, and remain a high CVD risk. Recently, several large randomized clinical trials have shown that the addition of PCSK9 inhibitors (PCSK9i) to statins lead to a further reduction in LDL-C and cardiovascular risk[31,32], even in HoFH/cHeFH patients that were characterized by high LDL-C levels and CVD risk[33,34]. In addition, PCSK9i showed anti-inflammatory and immunomodulatory effects in FH patients. Roberto et al.[35] found that in HeFH patients, six-month add-on PCSK9i significantly reduced LDL-C levels, neutrophils count and inflammatory marker MHR, while NLR was not altered. However, HoFH/cHeFH and HeFH usually respond differently to PCSK9i, and no data exist regarding the effects of PCSK9i on systemic inflammation in HoFH/cHeFH patients exclusively.

In the present study, we firstly described the systemic inflammation profile of HoFH/cHeFH patients, and then evaluated the effects of PCSK9i on these systemic inflammatory biomarkers at 3 months and 6 months after PCSK9i treatment.

Methods

Study design and participants

This study protocol was reviewed and approved by the ethics committees of Beijing Anzhen Hospital, Capital Medical University. All subjects voluntarily participated in the study and signed informed consent, and cooperated with the medical staff to complete the follow-up.

Eligible participants were HoFH/cHeFH patients diagnosed by genetic testing (two alleles both carry mutation in the region of LDLR, APOB, PCSK9 or LDLRAP1). The pathogenic genes were detected by the second-generation sequencing technique. Eligibility criteria were age between 12-75 years old; bodyweight ≥ 40kg; fasting triglyceride (TC) ≤ 4.5 mmol/L; and fasting LDL-C ≥ 3.4 mmol/L after at least 4 weeks of a stable high intensity statins plus ezetimibe therapies. Exclusion criteria included uncontrolled cardiac arrhythmias, myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass grafting, stroke, deep vein thrombosis, pulmonary embolism (< 3 months prior to study start), systolic blood pressure > 180mmHg and/or diastolic blood pressure > 110 mmHg, a confirmed or potential ineffectiveness of PCSK9i and had received other PCSK9i and cholesteryl ester transfer protein inhibitors (> 6 months prior to study start).

From May 2019 to August 2021, 62 probable HoFH/cHeFH patients were enrolled from Beijing Anzhen Hospital, Capital Medical University. All participants had received stable maximum statin therapy with ezetimibe at least 4 weeks (that is, atorvastatin 40mg/d or rosuvastatin 20mg/d, ezetimibe 10mg/d) before they started to add on PCSK9i 450mg administered subcutaneously every 4 weeks (Q4w). Biochemical analyses were performed at the day before PCSK9i administration (T0), 1 month (T1), 2 months (T2), 3 months (T3) and 6 months (T6) after the start of PCSK9i administration. At T3, the lipid-lowering effects of PCSK9i were evaluated. If they did not attain LDL-target, the follow-up would be terminated at T3. LDL-target was defined by the reduction of mean level of LDL-C at T1, T2 and T3 > 5% compared to T0. Others continued to receive follow-up visits.

The counts and percentages of neutrophils, lymphocytes and monocytes, serum TC, triglycerides (TG), LDL-C, high-density lipoprotein cholesterol (HDL-C), fasting plasma glucose (FPG), alanine transaminase (ALT), aspartate transaminase (AST), creatinine (CREA), platelets count and mean platelet volume (MPV) were assessed using a Roche COBAS 701 analyzer. NLR, PLR, MHR, MLR and MPVLR were calculated by the aforementioned value.

Statistical analysis

The continuous data are expressed as mean ± standard deviation (SD), and categorical data as frequency (percentage). SPSS software version 25.0 (SPSS, Inc., Chicago, IL) are used for statistical analyses. Normality distribution was determined by Kolmogorov-Smirnov test. For continuous variables that satisfy normal distribution, independent two-sample t-tests or paired t-test were used; otherwise, the Mann-Whitney U test was used. Categorical data were compared by Chi-square test. For all analyses, *P*-values < 0.05 were considered statistically significant.

Results

In our study, we evaluated 62 probable HoFH/cHeFH patients. Of these, 21 definitive patients that received stable maximum statins plus ezetimibe therapy at least one month started to add on PCSK9i 450mg Q4W and were followed up once a month until T6. Of these, two patients withdrew at T1; two patients withdrew at T2; four patients did not meet LDL-target and the follow-up was terminated at T3; and three patients withdrew at T4 (Figure 1). Meanwhile, 47 healthy donors (HD) were recruited as controls.

Baseline Characteristics Of The Participants Before Pcsk9i Therapy

The baseline characteristics of the participants before PCSK9i therapy were summarized in Table 1. Among 21 patients enrolled in our study, five patients had homozygous mutations (four in LDLR gene and one in LDLRAP1 gene), and 16 patients had compound heterozygous mutations (15 patients harbored two LDLR mutation sites; one patient had two mutation sites in LDLR gene, one mutation site in

APOB gene). Compared to HD, HoFH/cHeFH patients had dramatically higher levels of TC and LDL-C. Of note, HoFH/cHeFH patients displayed a disturbed blood biomarker profile. Among eight platelets and white blood cell (WBC) parameters, seven were significantly different between HoFH/cHeFH patients and HD, including increased MPV, neutrophil counts and percentages, decreased lymphocytes counts and percentages, monocyte percentages, as well as platelets counts in HoFH/cHeFH patients. The monocyte counts were comparable between HoFH/cHeFH patients and HD. The systemic inflammatory biomarkers NLR, MHR, MLR and MPVLR that derived from above parameters was significantly higher in HoFH/cHeH patients (76.22%, 117.78%, 27.27%, 30.22% higher than in HD, respectively).

Effects of PCSK9i therapy on inflammatory biomarkers in HoFH/cHeFH patients

After 3 months of add-on PCSK9i therapy, the levels of TC and LDL-C were significantly reduced by 14.15% and 21.14% (from 11.17±3.32 mmol/L to 9.59±3.56 mmol/L and from 9.65±3.24 mmol/L to 7.61±3.25 mmol/L, respectively). Meanwhile, four of seven above disturbed platelets and WBC parameters statistically recovered, including MPV, percentage and count of neutrophils, percentage of lymphocytes. Monocyte count significantly decreased after 3-month PCSK9i therapy. Furthermore, PCSK9i therapy reduced two inflammatory biomarkers NLR and MLR (-25.43% and -23.33%, respectively) (Table 2).

We further analyzed NLR and MLR of ten patients who completed 6 months therapy. We found that the LDL levels at T6 were lower than the levels before PCSK9i treatment. However, NLR and MLR at T6 returned to the levels of T0. Meanwhile, cell counts of monocytes and lymphocytes at T6 were statistically comparable to the levels before PCSK9i treatment (Figure 2).

Discussion

Being exposed to high LDL levels since birth, FH patients have high-risk of premature AS and CVD. Since AS and CVD are associated with hypercholesterolemia-induced inflammation, anti-inflammatory effects of lipid lowering drugs should receive great attention[36]. In general, the lipid-lowering effect of statins differs between HeFH and HoFH/cHeFH[37]. Around 20% HeFH can meet LDL-target after the use of statins[38], while LDL levels in most HoFH patients merely attained around 10 mmol/L even with highest doses of most efficacious statins[5]. In the present study, we enrolled 21 HoFH/cHeFH patients with maximum tolerated statin dose plus ezetimibe. These patients had higher LDL-C levels than HD (9.70±3.62 mmol/L vs 1.36±0.30 mmol/L), and displayed a hyper-inflammatory state, as indicated by an abnormal blood biomarker profile that related to neutrophils, monocytes, lymphocytes and platelets.

Previous studies have shown that combination therapy of PCSK9i and statins can further reduce LDL-C by 45.7%[39] and 23.1%[33] for HeFH and HoFH/cHeFH patients, respectively. Consistently, we found a significant reduction in LDL-C (from 9.65±3.24 mmol/L to 7.61±3.25 mmol/L) after adding-on three-month PCSK9i. Although the levels of LDL-C at this time-point (T3) did not achieve LDL target recommended by ECS guidelines[28], the blood biomarker profile was partially recovered. This finding is

consistent with previous studies that revealed the relation between PCSK9 and chronic inflammation[40,41]. To the best of our knowledge, our study first reported the effects of PCSK9i on systemic inflammatory status in HoFH/cHeFH patients exclusively.

It should be emphasized that NLR and MLR were significantly reduced after three-month add-on PCSK9i therapy. Since lymphocyte counts were comparable during this period, the reduction of NLR and MLR should be attributed to a significant decrease in neutrophil counts (from 7.27±3.94 to 4.54±1.32 $\times 10^9$/L) and monocyte counts (from 0.76±0.50 to 0.47±0.14 $\times 10^9$/L). Although further investigations are still needed, several studies have provided clues that PCSK9i alters systemic inflammation levels through regulating neutrophils and monocytes. Clinical trials found that the concentration of PCSK9 in serum was positively correlated with neutrophils and lymphocytes numbers in CAD patients[42]. Bernelot *et al*.[43] reported that monocytes pro-inflammatory phenotypes of FH were reversed after 24-week PCSK9i treatment, as shown by the decreased monocytes migration capacity and inflammatory responses. The role of monocytes and macrophages has been extensively studied in AS. There are growing evidence suggesting that neutrophils also contribute to cardiovascular inflammation and development of atherosclerotic plaques[44,45]. For example, neutrophils stimulate the activation and dysregulation of the endothelial cell through secreting reactive oxygen species (ROS)[46] and myeloperoxidase (MPO)[47]. MPO also mediate oxidation of LDL, promoting the formation of foam cells.

Unfortunately, we noticed that at 6-month after PCSK9i treatment, NLR and MLR returned to pre-PCSK9i treatment levels. It would be of great interest to investigate why PCSK9i induces a transient decrease in NLR and MLR and whether HoFH/cHeFH patients with reduction of NLR or MLR might have more potential to gain benefit from PCSK9i therapy. Our present study was limited by the case number. In-depth investigation regarding changes in neutrophils function should be conducted in the further studies.

Conclusions

In HoFH/cHeFH patients, PCSK9i induces a transient decrease in systemic inflammatory biomarker NLR and MLR. We notice that NLR and MLR are reduced after 3-month PCSK9i therapy, while returned to the baseline levels after 6-month PCSK9i therapy. These transient changes are mostly attributed to the changes of neutrophil and monocytes counts. Our results add evidence in evaluating the effects of PCSK9i on systemic inflammation.

Abbreviations

HoFH/cHeFH
Homozygous/compound heterozygous familial hypercholesterolemia
TC
total cholesterol
TG
triglycerides

HDL-C
high-density lipoprotein cholesterol
LDL-C
low-density lipoprotein-cholesterol
FPG
fasting plasma glucose
ALT
alanine transaminase
AST
aspartate transaminase
CREA
creatinine
MPV
mean platelet volume
AS
atherosclerosis
CVD
cardiovascular diseases
LDLR
LDL-receptor
APOB
apolipoprotein B
PCSK9
proprotein convertase subtilisin/kexin-9
LDLRAP1
low-density lipoprotein receptor adaptor protein 1
PCSK9i
PCSK9 inhibitor
NLR
neutrophil-lymphocyte ratio
PLR
platelet-lymphocyte ratio
MHR
monocyte-HDL ratio
MLR
monocyte-lymphocyte ratio
MPVLR
mean platelet volume-lymphocyte ratio
ROS
reactive oxygen species

MPO
myeloperoxidase

Declarations

Ethics approval and consent to participate

This study protocol was reviewed and approved by the ethics committees of Beijing Anzhen Hospital, Capital Medical University. The consent was signed by all the participants prior to their enrollment in the study.

Consent for publication

Not applicable.

Availability of data and materials

All data generated and analyzed in this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

F.L.,P.Y.: Acquisition of data and writing; Y,H.,J.D.,H,Z.,Z.W.,X.W.,Y.M.: Analysis, interpretation of data, and technical, material support; H.Z.,J.L.: Study supervision and revision of the manuscript. All authors read and approved the final manuscript.

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Figures

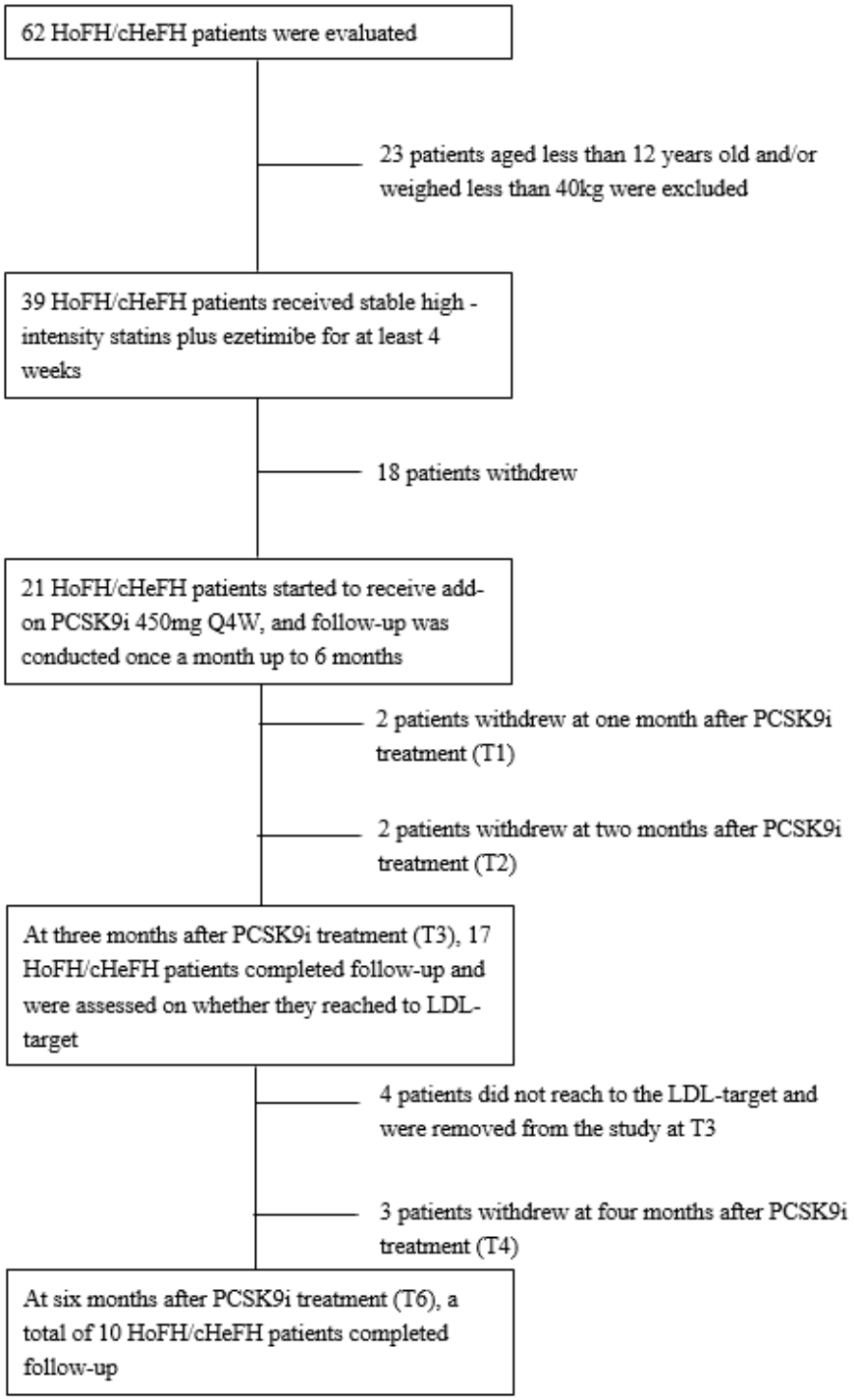

Figure 1

Study population flowchart

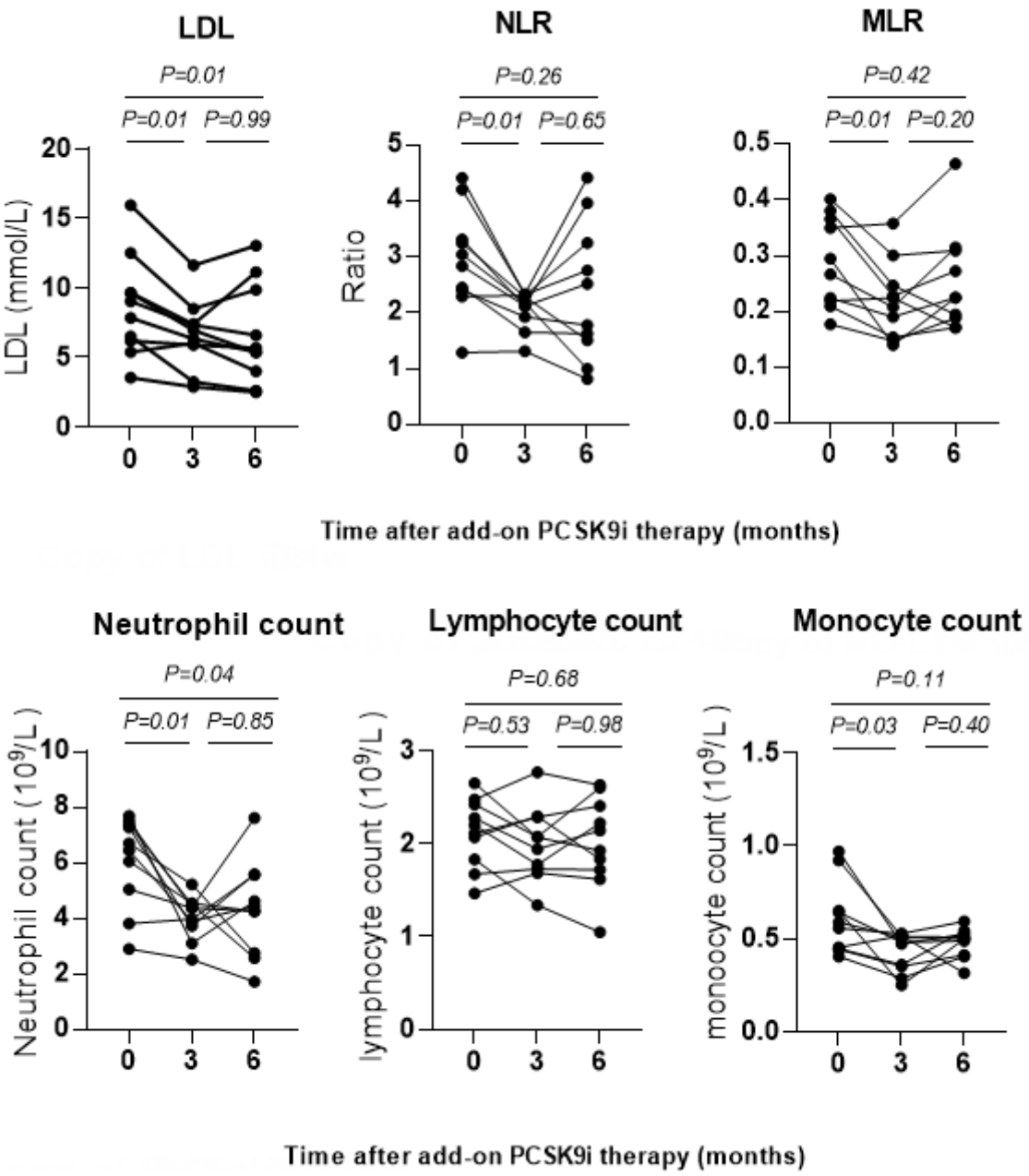

Figure 2

The levels of LDL, NLR, MLR, Neutrophil count, Lymphocyte count, Monocyte count at before PCSK9i treatment, 3 months and 6 months after PCSK9i treatment