British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2017) **83** 1002–1010 1002

CLINICAL TRIALS

Extended-release niacin increases anti-apolipoprotein A-I antibodies that block the antioxidant effect of high-density lipoprotein–cholesterol: the EXPLORE clinical trial

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Received 29 August 2016; **Revised** 18 October 2016; **Accepted** 14 November 2016

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Keywords antibodies, antioxidant, apoliproteins, high-density lipoprotein, immune system

AIMS

Extended-release niacin (ERN) is the most effective agent for increasing high-density lipoprotein–cholesterol (HDL-C). Having previously identified anti-HDL antibodies, we investigated whether ERN affected the antioxidant capacity of HDL and whether ERN was associated with the production of antibodies against HDL (aHDL) and apolipoprotein A-I (aApoA-I).

METHODS

Twenty-one patients older than 18 years, with HDL-C ≤40 mg dl^{-1} (men) or ≤50 mg dl^{-1} (women) were randomly assigned to receive daily ERN (n = 10) or placebo (n = 11) for two sequential 12-week periods, with 4 weeks of wash-out before cross-over. Primary outcome was change of paraoxonase-1 (PON1) activity and secondary outcomes were changes in aHDL and aApoA-I antibodies. Clinical Trial Unique Identifier: EudraCT 2006–006889-42.

RESULTS

The effect of ERN on PON1 activity was nonsignificant (coefficient estimate 20.83 U l^{-1}, 95% confidence interval [CI] –9.88 to 51.53; P = 0.184). ERN was associated with an increase in HDL-C levels (coefficient estimate 5.21 mg dl^{-1}, 95% CI 1.16 to 9.25; P = 0.012) and its subclasses HDL2 (coefficient estimate 2.46 mg dl^{-1}, 95% CI 0.57 to 4.34; P = 0.011) and HDL3 (coefficient estimate 2.73 mg dl^{-1}, 95% CI 0.47 to 4.98; P = 0.018). ERN was significantly associated with the production of aApoA-I antibodies (coefficient estimate 0.25 μg ml^{-1}, 95% CI 0.09–0.40; P = 0.001). aApoA-I titres at baseline were correlated with decreased PON activity.

CONCLUSIONS

The rise in HDL-C achieved with ERN was not matched by improved antioxidant capacity, eventually hampered by the emergence of aApoA-I antibodies. These results may explain why Niacin and other lipid lowering agents fail to reduce cardiovascular risk.

DOI:10.1111/bcp.13198

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- High-density lipoprotein–cholesterol (HDL-C) is associated with a reduced cardiovascular risk.
- Extended-release niacin (ERN) is the most effective agent for increasing HDL-C levels.
- Clinical studies have not shown a reduction in cardiovascular events by HDL-increasing therapies – the "HDL paradox".

WHAT THIS STUDY ADDS

- Increased anti-apolipoprotein A-I titres were observed after only 12 weeks of ERN treatment, and were correlated with HDL-C levels.
- This could lead to reduced biological activity of HDL particles, hampering the protective effect of the increased HDL mass.
- These results suggest a new mechanism that explains the clinical inefficacy of ERN.

Table of Links

LIGANDS
Nicotinic acid

This Table lists key ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1].

Introduction

Atherosclerosis is a leading cause of cardiovascular morbidity and mortality. Despite a dramatic reduction in low-density lipoprotein–cholesterol (LDL-C), treatment with statins is still associated with a persistent cardiovascular risk [2]. The protective role of high-density lipoprotein–cholesterol (HDL-C) against atherosclerosis has been extensively suggested [3], but a clear clinical effect for a persistent increase of HDL-C is yet to be shown. Extended-release niacin (ERN) is the most powerful drug in current clinical practice to increase HDL-C (up to 35%) [4]. It also reduces triglycerides (TG), lipoprotein (a) and LDL-C, favourably changing the size and number of LDL particles [5]. Furthermore, ERN also differentially changes the relative quantity of different HDL subfractions, which could increase its antiatherogenic action. Although the mechanisms by which ERN operates these changes on HDL are not fully understood, it is thought to reduce the availability of free fatty acid for hepatic VLDL synthesis, leading to reduced cholesteryl ester transfer protein activity and increased HDL2/HDL3 ratio [6]. Additionally, it could also decrease the hepatic uptake of HDL particles [7]. HDL2 has a higher content of apolipoprotein A-I (ApoA-I), which is associated with an increase in paraoxonase-1 (PON1) activity [8]. PON1 is an important component of HDL particles, which can metabolize lipid peroxides, not only inside the HDL particle but also in other lipoproteins (such as LDL), and even in the atherosclerotic plaque. Furthermore, PON1 activity has been shown to be reduced in several diseases associated with a high cardiovascular risk, such as diabetes mellitus or renal failure [9].

This "HDL-paradox" has been highlighted by four clinical trials in patients with optimized LDL-C levels, in whom the rate of cardiovascular events did not reduce, despite an increase in HDL-C levels and regardless of the treatment used [10–14].

Previously, our group has identified antibodies against HDL (aHDL), which may be a "family" of autoantibodies with different targets within the lipoprotein that can impair HDL function [15–18]. We hypothesize that aHDL, or specifically anti-ApoA-I antibodies (aApoA-I), may be induced by HDL-C-boosting treatments, thus hampering the antiatherogenic effects expected as a consequence of higher serum HDL-C levels.

In this study, we aimed to determine the effect of ERN on the antioxidant capacity of HDL as well as on the production of aHDL and aApoA-I antibodies, and whether the presence of the latter was associated with a reduction in HDL's antioxidant activity.

Methods

Study design and participants

This is an exploratory phase II, randomized, double-blind placebo controlled, single cross-over, investigator initiated trial conducted in NOVA Medical School, Universidade Nova de Lisboa, Portugal. The study was approved by the Portuguese National Ethics Committee for Clinical Investigation (reference number CEIC 0702BU063), and was performed according to the principles of the Declaration of Helsinki and Good Clinical Practice. The trial was registered with EudraCT as number 2006–006889-42.

Eligible participants were men or women of any ethnic origin, aged 18 years or older, with serum HDL-C $\leq$40 mg dl^{-1} or $\leq$50 mg dl^{-1}, respectively. Participants were excluded if they had: allergy to the study drug; a physical or psychological condition compromising their participation in the trial; a treatment regimen with statins, fibrates or other lipid-lowering medication during the 8 weeks prior to enrolment; serum LDL-C >180 mg dl^{-1}; TG >200 mg dl^{-1}; diabetes

mellitus or cardiovascular disease; an active peptic ulcer; an active haemorrhage; a history of drug abuse (except alcohol); creatinine clearance <60 ml min^{-1}, total bilirubin ≥2 times the upper limit of normal; aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≥3 times the upper limit of normal; participation in another investigational drug trial within 30 days of enrollment. Women who were pregnant, nursing, planning to become pregnant while in the trial or unable to use effective contraception were excluded.

Patients were recruited from local hospitals and clinics, and invited to participate in the study, which was performed at NOVA Medical School, Universidade Nova de Lisboa. All patients provided written informed consent.

Randomization and masking

Participants were randomly assigned (1:1) using stratified permuted blocks. Each randomization block was composed of six patients, with three patients per treatment sequence (A: ERN/Placebo; B: Placebo/ERN). A list generated by an independent clinical research organization (Keypoint Group, Portugal), contained a code number that identified the sequence assigned to each patient included in the trial. A paper copy of the randomization code list was placed in a sealed opaque envelope and provided to the Responsible Pharmacist in order to allow for the preparation of the study drugs and placebos. Individual sealed opaque code envelopes together with written instructions for code breaking were provided to the investigator. Physicians who enrolled participants, using the sequence generated by the CRO to assign them to the trial groups, were responsible for all assessments carried out during the study. ERN and placebo tablets were identical in appearance. Patients, those carrying out interventions (physicians) and those assessing outcomes (laboratory investigators) were masked to treatment assignment. Lipid measurements and the remaining laboratory assessments were performed by different laboratory investigators. Those analysing the final data were unblinded.

Study procedures

The study drug was taken orally, daily, at night, for 12 weeks, at an initial dose of 500 mg, which was titrated to a maximum dose of 1500 mg in the first 7 weeks. After a 4-week wash-out period (which is considered sufficient considering pharmacokinetic data about ERN and HDL particles), treatment arms were crossed over and placebo or ERN were given for an equivalent period of time, followed by a final assessment of safety and efficacy, 4 weeks after the end of treatment. All participants received dietary counselling during the study.

A general evaluation with records of demographics, medical history, concomitant medication and physical examination, which included height, weight, abdominal perimeter and blood pressures (variables measured by trained physicians), was performed at baseline and, with the exception of demographics and medical history, all other data (including change in concomitant medication or adverse events) were recorded at every study visit. Serum target parameters were assessed at baseline, then at weeks 7, 12, 16, 23, 28 and 32. They included: PON1 activity, nitric oxide metabolites (NO_2^- and NO_3^-), total cholesterol (TC), LDL-C and triglycerides (TG), very low-density lipoprotein-cholesterol (VLDL-C), total HDL-C, HDL2 and 3, ApoA-I and immunoglobulin (Ig)G aHDL and aApoA-I antibodies. TC, HDL-C, LDL-C and TG were determined by a colorimetric standard enzymatic reaction (commercial kits: Irlandox; Randox, Porto, Portugal). VLDL-C was estimated by dividing TG values by 5 (for TG levels ≤400 mg dl^{-1}). HDL subfractions 2 and 3 were determined by an enzymatic assay using a QUANTILOP HDL (HDL2/HDL3) precipitation test reagent. ApoA-I serum concentration was measured by an immunoturbidimetric immunoassay (commercial kits: Randox). PON1 activity was assessed by quantification of nitrophenol formation by spectrophotometry [19]. Serum nitric oxide metabolites (NO_2^- and NO_3^-) were measured using a modified Griess reaction [20]. Titres of IgG aHDL and IgG aApoA-I antibodies were assessed by an enzyme-linked immunosorbent assay as previously described [16–18].

Outcomes

Primary outcome was change of mean PON1 activity in serum from baseline to end of treatment. Secondary endpoints included changes in lipid profile, aHDL and aApoA-I antibodies and mean serum nitric oxide metabolites.

Safety parameters (full blood count and basic chemistry) and a 12-lead electrocardiogram were performed at baseline and at weeks 16 and 32. All adverse events were recorded.

Data management

Data collection, management and monitoring were conducted by an independent clinical research organization (Keypoint Group, Portugal).

Statistical analysis

We calculated that a sample size of 30 patients in this two-treatment crossover study would provide 80% power to detect a difference in mean PON1 activity of 250 U l^{-1} between the treatments, at a significance level $\alpha = 0.05$. We initially aimed to randomize 36 patients with an assumed dropout rate of 15%. We did intention-to-treat and per protocol analyses; in the latter, we compared outcomes amongst participants who were compliant with treatment. Compliance was determined before data reviewing or unmasking. Subjects who had taken <80% or >120% of the overall prescribed medication during the active treatment phase were regarded as noncompliant and were excluded from the per protocol analysis. Plasma pharmacokinetic measurements of the study drug were not undertaken.

Summary statistics for categorical variables were presented by frequencies (*n*) and percentages (%) and continuous variables were described using mean and standard deviation or 95% confidence interval, when applicable. Baseline characteristics between the two groups were analysed using the Mann–Whitney test (continuous data) and Fisher's test (categorical variables). Primary and secondary efficacy analyses were performed based on the per protocol population. To compare treatment effects, linear mixed models were built to take into account the autocorrelation structure between longitudinal measures. The linear mixed effects models were fitted for all outcomes separately. Individual effect was considered random and fixed effects were treatment regimen, period effect, baseline measurements and carryover

effect. Data were pooled between the two treatment phases after finding no carryover effect. Spearman coefficients were calculated to analyze correlations between IgG aApoA-I antibodies and PON1 activity, HDL-C and its subfractions, and IgG aHDL antibodies, before and after treatment with ERN. A significance level $\alpha = 0.05$ was considered. All data were analysed using STATA 13.0. (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.) and SPSS (Version 21.0) software.

The trial was registered with EudraCT: number 2006–006889-42.

Results

Between March 1, 2008 and November 30, 2008, we randomly assigned 21 participants to the placebo group ($n = 11$) or the ERN group ($n = 10$), of whom only 17 (81%) completed the study. Two patients from the placebo group abandoned clinical follow-up and two patients from ERN group discontinued treatment due to the occurrence of adverse events. In both groups, these patients left the study before reaching the end of the first period of treatment, so they were excluded from the final analysis (Figure 1). Baseline demographics, anthropometry, medical history, lipid profile and biological variables were similar in both groups (Table 1). Regarding safety assessments, no significant differences were observed between groups. No severe adverse events were reported. As the results from the intention-to-treat and per protocol analyses were similar, we will only consider the latter.

Effect of ERN treatment on the lipid profile

Patients treated with ERN had a mean estimated increase of 5.21 mg dl^{-1} (95% confidence interval [CI] 1.16 to 9.25; $P = 0.012$) in HDL-C levels, which corresponds to a relative change of 15.63% in the ERN group, compared to 1.51% in the placebo cohort (Table 2). Treatment with ERN was also associated with a mean estimated increase of 2.46 mg dl^{-1} (95% CI 0.57 to 4.34; $P = 0.011$) in HDL2 levels and 2.73 mg dl^{-1} (95% CI 0.47 to 4.98; $P = 0.018$) in HDL3, corresponding to a relative change of 35.73% and 11.96% in the ERN group and to a relative change of –2.05% and 3.47% in the placebo group, respectively. Although not statistically significant, levels of total cholesterol ($P = 0.555$), LDL-C ($P = 0.298$), TG ($P = 0.167$) and VLDL ($P = 0.167$) decreased in the ERN group when compared to placebo.

Effect of ERN treatment on the HDL antioxidant function and in the levels of anti-HDL antibodies

No significant effect on PON1 activity was observed after treatment with ERN in comparison to placebo (Table 2).

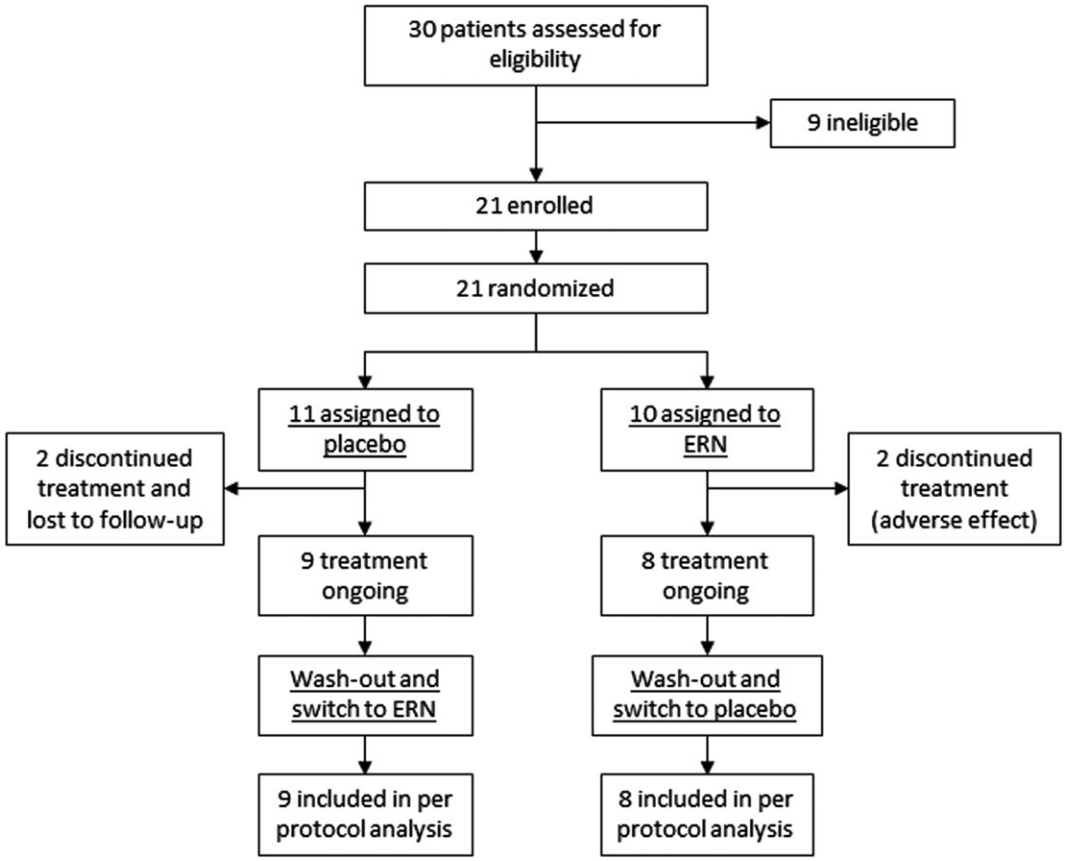

Figure 1
Study flow diagram

Table 1

Baseline demographic characteristics, clinical and serological data of the two groups

Characteristics[a]	Placebo(*n* = 9)	ERN(*n* = 8)	*P*-value[b]
Age, y	52.44 (9.55)	46.13 (12.02)	0.248
Sex, female/male *n* (%)	3 (33.33) / 6 (66.67)	3 (37.50) / 5 (62.50)	1.000
Ethnic origin, black/Caucasian, *n* (%)	1 (11.11) / 8 (88.89)	0 (0.00)/ 8 (100.00)	1.000
Weight, kg	78.78 (13.51)	82.00 (12.21)	0.500
Height, cm	164 (9.00)	171 (11.00)	0.311
Body mass index, kg m^{-2}	29.09 (3.20)	28.09 (4.68)	0.541
Systolic blood pressure, mmHg	125.78 (14.54)	128.75 (11.86)0	0.629
Diastolic blood pressure, mmHg	75.67 (10.02)	77.50 (6.19)	0.884
Medical history			
Hypertension, *n* (%)	4 (44.44)	2 (25.00)	0.619
Cerebrovascular disease, *n* (%)	1 (11.11)	0 (0.00)	1.000
Others, *n* (%)	4 (44.44)	2 (25.00)	0.619
Lipid profile			
LDL cholesterol, mg dl^{-1}	138.11 (24.85)	135.75 (23.58)	0.736
Total cholesterol, mg dl^{-1}	198.22 (31.34)	207.38 (30.51)	0.500
Triglycerides, mg dl^{-1}	134.33 (40.71)	127.50 (46.02)	0.847
VLDL cholesterol, mg dl^{-1}	26.84 (8.11)	25.63 (9.22)	0.885
HDL cholesterol, mg dl^{-1}	33.72 (5.74)	34.10 (5.92)	1.000
HDL2, mg dl^{-1}	6.87 (2.25)	6.50 (2.11)	0.885
HDL3, mg dl^{-1}	26.86 (4.47)	27.61 (4.39)	0.923
Apolipoprotein A-I, mg dl^{-1}	133.78(16.62)	130.31 (12.63)	0.773
Biological variables			
PON1 activity (U l^{-1})	344.47 (94.13)	347.30 (97.74)	1.000
NO_2^- + NO_3^- (μmol l^{-1})	52.32 (34.72)	52.41 (46.10)	0.606
IgG aHDL (% p. control)	123.42 (64.52)	162.35 (131.66)	0.743
IgG aApoA-I (μg ml^{-1})	0.40 (0.18)	0.30 (0.09)	0.135

[a]Data are expressed as mean (standard deviation) for continuous data and frequencies (%) for categorical variables.
[b]Differences between means were evaluated using Mann–Whitney (continuous data) and Fisher's exact test (categorical variables).
aApoA-I, anti-apolipoprotein A-I antibodies; aHDL, anti-HDL antibodies; ERN, extended-release niacin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NO_2^- + NO_3^-, nitric oxide metabolites; PON1, paraoxonase 1; VLDL, very low-density lipoprotein

Levels of IgG aApoA-I antibodies had a mean estimated increase of 0.25 μg ml^{-1} (95% CI 0.09–0.40; P = 0.001) after treatment with ERN, equivalent to a relative change of 93.16% compared with 6.17% in the placebo group. Although the titres of IgG aHDL antibodies did not differ between treatment arms, at the end of treatment there was a positive correlation between these antibodies and aApoA-I antibodies (r = 0.53, P = 0.03; Figure 2A,B), and between HDL2 and IgG aApoA-I (r = 0.61, P = 0.009; Figure 2C,D) in subjects treated with ERN. These subjects also presented a negative correlation between PON1 activity and IgG aApoA-I titres at baseline (r = –0.50 P = 0.04), which was lost at the end of treatment (Figure 2E,F).

No significant differences were found in nitric oxide metabolites levels (P = 0.589) between groups at the end of study, nor any association with lipid profile or other biological variables (Table 2).

Discussion

In this pilot trial, ERN administered for the trial period was associated with an increase in HDL-C, HDL2 and HDL3 when compared to placebo. Patients treated with ERN had significantly higher titres of IgG aApoA-I antibodies, which were positively correlated with both HDL2 and IgG aHDL at the end of treatment. Regarding PON1 and NO metabolites, known as important players in the antioxidant and antiatherogenic actions of HDL, there were no significant differences between the two groups. These findings suggest that

Table 2

Effect of 12 weeks of treatment with ERN on the study target parameters

	Placebo		ERN		ERN treatment effect	
Outcomes[a]	**Baseline**	**EOT**	**Baseline**	**EOT**	**Coeficient estimate (95%CI)**	***P*-value**[b]
LDL cholesterol, mg dl^{-1}	132.47 (31.20)	140.00 (26.61)	141.53 (25.37)	131.59 (31.18)	–7.47 (–21.55 to 6.61)	0.298
Total cholesterol, mg dl^{-1}	199.82 (27.63)	200.67 (35.73)	206.18 (28.60)	196.65 (42.46)	–5.88 (–25.41 to 16.65)	0.555
Triglycerides, mg dl^{-1}	127.47 (52.71)	148.40 (59.81)	151.94 (67.86)	127.18 (67.51)	–21.06 (–50.96 to 8.84)	0.167
VLDL cholesterol, mg dl^{-1}	25.45 (10.54)	29.68 (11.93)	30.47 (13.57)	25.53 (13.42)	–4.21 (–10.19 to 1.77)	0.167
HDL cholesterol, mg dl^{-1}	35.67 (7.40)	35.67 (6.74)	34.25 (4.58)	39.80 (9.30)	5.21 (1.16 to 9.25)	0.012[c]
HDL2, mg dl^{-1}	7.69 (2.86)	7.19 (2.46)	6.38 (1.68)	8.59 (3.82)	2.46 (0.57 to 4.34)	0.011[d]
HDL3, mg dl^{-1}	27.97 (5.05)	28.47 (5.17)	27.88 (3.69)	31.20 (6.02)	2.73 (0.47 to 4.98)	0.018[e]
Apolipoprotein A-I, mg dl^{-1}	135.91 (18.16)	136.90 (18.66)	133.26 (10.95)	133.50 (23.49)	–4.47 (–12.03 to 3.09)	0.246
PON1 activity (U l^{-1})	333.09 (101.84)	329.06 (98.65)	331.25 (97.96)	349.01 (111.50)	20.83 (–9.88 to 51.53)	0.184
NO_2^- + NO_3^- (μmol l^{-1})	52.87 (37.01)	45.84 (35.05)	55.75 (38.80)	54.10 (53.68)	–8.52 (–39.48 to 22.43)	0.589
IgG aHDL antibodies (%p. control)	126.47 (67.30)	116.46 (84.15)	132.52 (101.63)	127.25 (61.33)	13.05 (–9.53 to 35.62)	0.257
IgG aApoA-I antibodies (μg ml^{-1})	0.36 (0.14)	0.35 (0.07)	0.33 (0.11)	0.59 (0.32)	0.25 (0.09 to 0.40)	0.001

[a]Data are expressed as mean (standard deviation).
[b]ERN treatment effect was calculated using linear mixed effects models and is presented as coefficient estimate (95% confidence interval).
[c]HDL cholesterol levels at baseline remained in the multivariable model;
[d]Period effect and HDL2 levels at baseline remained in the multivariable model;
[e]HDL3 levels at baseline remained in the multivariable model.
aApoA-I, anti- apolipoprotein A-I antibodies; aHDL, anti-HDL antibodies; EOT, end of treatment; ERN, extended-release niacin; HDL, highdensity lipoprotein; LDL, low-density lipoprotein; NO_2^- + NO_3^-, nitric oxide metabolites; PON1, paraoxonase 1 and VLDL, very low-density lipoprotein.

the increase in HDL-C, HDL2 and HDL3 levels obtained with ERN did not translate into an increase in the protective capacity of HDL. By allowing also the enhancement of IgG aApoA-I antibodies, ERN might be contributing to an overall final impairment of HDL's antioxidant function.

Anti-HDL antibodies are a family of antibodies, the specificity of which is directed against ApoA-I and PON1 [15–18]. They have been reported in patients with diabetes [21], cerebrovascular and cardiovascular diseases [22, 23], Alzheimer's disease [24] and in different autoimmune conditions [15–17, 25, 26]. They are biologically active [27, 28], and our group has shown that they can inhibit the physiological properties of HDL in experimental models [18, 29, 30]. Furthermore, different antibody profiles seem to be associated with different clinical phenotypes [18].

In this study, there was a significant and robust increase of the titres of aApoA-I antibodies in the treatment arm. The fact that after treatment, and not at baseline, the titres of aApoA-I antibodies and of IgG aHDL were positively correlated, suggests that after ERN administration the majority of aHDL antibodies are directed against aApoA-I. This might be associated with a predominance of ApoA-I as an immunogenic particle, or with increased immunogenicity of the existent ApoA-I molecules. Interestingly, ApoA-I levels were unchanged between treatment arms, which could be related to enhanced clearance mediated by the increased level aApoA-I antibodies, or could support the latter hypothesis.

Nevertheless, the increased aApoA-I titres after ERN treatment could explain why PON activity did not parallel the increase in HDL, as PON needs ApoA-I to stabilize and improve its antioxidant activity [31]. Accordingly, aApoA-I titres at baseline were associated with a reduced PON activity. However, that correlation, although apparent, did not reach statistical significance at the end of treatment. This could be due to a low sample size, which was not powered to detect this secondary outcome. Alternatively, a weakening of that correlation could be explained by a saturation of the inhibitory effect of aApoA-I on the PON enhancement by ApoA-I. In this scenario, upon high aApoA-I titres, PON activity would be further hampered only by the anti-PON1 fraction of aHDL, which is expected to be lower after ERN. Lastly, the possibility that aApoA-I would lose its biological activity after ERN treatment seems more bizarre and would not explain the clinical data.

Currently, translational research on HDL shows an absence of positive results in clinical-focused trials on drugs that increase HDL-C levels. This "HDL-paradox" highlights the clear contrast between the protective effects of HDL in basic-research settings and its inefficacy in clinical trials. The present results suggest a viable explanation for such a disparity.

There are some limitations to this study: the sample was small and the duration of treatment short. Nevertheless, these limitations would have favoured a negative result, with a low probability of a functionally relevant production of

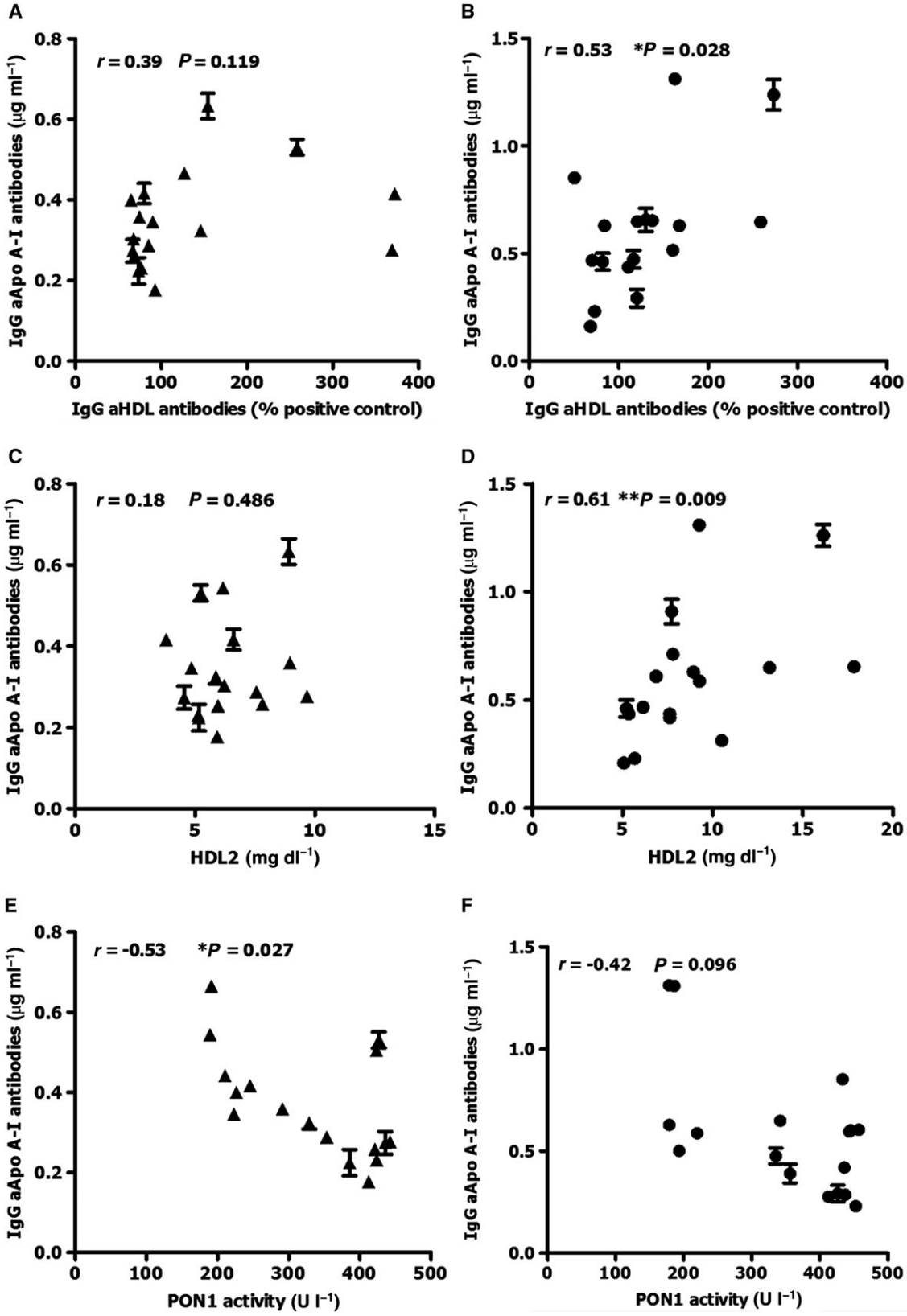

Figure 2

Correlation between anti-apolipoprotein A-I antibodies titres and target parameters at baseline and end of treatment in ERN group. Spearman's correlation between IgG anti-apolipoprotein A-I (aApoA-I) and IgG anti-high density lipoprotein (aHDL) antibodies at (A) baseline and (B) the end of treatment, HDL2 levels at (C) baseline and (D) the end of treatment and paraoxonase 1 (PON1) activity at (E) baseline and (F) end of treatment

antibodies in such a short period of time. The significant increase of HDL-C, HDL2 and HDL3 unmatched by an increase in the functional activity of HDL points towards the neutralizing capacity hence the relevance of these antibodies. Additionally, plasma pharmacokinetic measurements were not made, which could have improved the determination of compliance to the study drug.

The effect of lipid-modifying agents on antibodies toward HDL components had never been studied. We put forward the possibility that under oxidative and proinflammatory setting, a drug-induced increase in HDL-C concentrations could lead to increased aHDL or aApoA-I antibody production, thus abrogating the expected clinical results in trials on niacin. This may be a major breakthrough in understanding why treatments targeting HDL-C have not been effective in the clinical setting. Identifying patients with aApoA-I antibodies as well as defining their pathogenic role may help to design better trials and find better strategies for HDL-C interventions in the future.

Competing Interest

There are no competing interests to declare.

The authors would like to thank Merck KGaA for supplying the active and placebo treatment; the supplier had no role in the study design, data collection, data analysis, data interpretation or writing of the report. We also thank KeyPoint group in Portugal for their support in collection and management of the data.

This work was supported by NOVA Medical School | Faculdade de Ciências Médicas, Universidade NOVA de Lisboa; the funder of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Contributors

J.R.B., M.C.A., C.F. and J.D.A. contributed to the conception and design. J.R.B., M.C.A., C.F., F.S.P. and A.L.P. contributed to the acquisition, analysis or interpretation of data. J.R.B. and M.C.A. drafted the manuscript. All authors critically reviewed the work for important intellectual content.

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