Cardiovasc Drugs Ther (2011) 25:539–544
DOI 10.1007/s10557-011-6344-2

Anti-Inflammatory Effects of Varespladib Methyl in Diabetic Patients with Acute Coronary Syndrome

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Published online: 12 October 2011

Abstract
Purpose Secretory phospholipase A_2 group IIA ($sPLA_2$–IIA) concentration and activity are associated with increased risk of cardiovascular events in acute coronary syndrome (ACS) patients. This study evaluated baseline differences in $sPLA_2$-IIA concentration and other inflammatory markers in ACS patients with and without diabetes, and the inflammatory biomarker response to selective $sPLA_2$ inhibition.
Methods The effects of the $sPLA_2$ inhibitor varespladib methyl 500 mg daily and placebo on serial changes in inflammatory and lipid biomarkers were examined in 624 ACS patients who were treated with standard of care including atorvastatin 80 mg daily.
Results Compared with non-diabetic patients, diabetic patients had higher baseline concentrations of $sPLA_2$-IIA (p=0.0066), hs-CRP (p=0.0155), and IL-6 (p=0.009). At 8 weeks of treatment (primary endpoint), varespladib methyl reduced median $sPLA_2$-IIA levels by -83.6% in diabetic patients and by −82.4% in non-diabetic patients (p=0.33). Median hs-CRP and IL-6 levels were reduced in both varespladib methyl-treated diabetic and non-diabetic patients, but these differences were not statistically significantly different at 8 weeks (p=0.57 and p=0.97 respectively).
Conclusions Varespladib significantly reduces the post-ACS inflammatory response in those with and without diabetes. These responses were greater in diabetic subjects compared to non-diabetic subjects.

Key words Acute coronary syndromes · Lipoproteins · Phosphatases · Cytokines · Risk factors

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Background

Low-grade inflammation has been implicated in the pathogenesis of rupture-prone atherosclerotic lesions, which are more common in patients with diabetes than without diabetes [1–4]. High levels of high-sensitivity C-reactive protein (hs-CRP), a non-specific systemic inflammatory marker, are associated with higher risk of cardiovascular events in type 2 diabetes; [5, 6] however, elevated hs-CRP levels do not differentiate risk in ACS patients with and without diabetes [7, 8].

Secretory phospholipase A_2 ($sPLA_2$) represents a family of isoenzymes that contribute directly and indirectly to atherosclerosis [9]. The culprit coronary atherosclerotic lesions of patients presenting with acute myocardial infarction contain $sPLA_2$ group IIA ($sPLA_2$-IIA), which is detected both intracellularly in intimal macrophages and vascular smooth muscle cells and in extracellular deposits [10]. High $sPLA_2$-IIA levels and increased $sPLA_2$ activity identify ACS patients with increased cardiovascular events and all-cause mortality [11–16].

We hypothesized that ACS patients with diabetes have higher levels of $sPLA_2$-IIA and other inflammatory markers than non-diabetic patients, and that they would have an enhanced anti-inflammatory response to selective $sPLA_2$ inhibition with varespladib methyl. This hypothesis was tested by performing a sub-group analysis of the data from the Fewer Recurrent Acute Coronary events with Near-term Cardiovascular Inflammation Suppression (FRANCIS) trial [17].

Methods

The design of FRANCIS (*NCT00455546*) has been reported previously [17]. Briefly, 624 patients with ACS were randomized and treated with varespladib methyl (500 mg daily) or placebo within 96 h of a qualifying ACS event and were followed for a minimum of 6 months. All patients were treated with atorvastatin 80 mg daily. The primary endpoint

Table 1 Demographic and baseline characteristics

Variable	Diabetes group Varespladib methyl 500 mg + Atorvastatin 80 mg *N*=84	Diabetes group Placebo + Atorvastatin 80 mg *N*=87	Diabetes group Treatment p-value for Diabetics	Non-diabetes group Varespladib methyl 500 mg + Atorvastatin 80 mg *N*=229	Non-diabetes group Placebo + Atorvastatin 80 mg *N*=224	Non-diabetes group Treatment p-value for Non-Diabetics	p-value Diabetics vs. Non-Diabetics
Age (years), mean (SD)	60.8 (9.4)	62.8 (9.1)	0.16	57.6 (10.5)	58.4 (10.8)	0.48	<0.0001
Gender (%)							
Male	54 (64.3%)	60 (69.0%)	0.52	176 (76.9%)	176 (78.6%)	0.66	0.005
Female	30 (35.7%)	27 (31.0%)	–	53 (23.1%)	48 (21.4%)	0.66	–
Caucasian, n (%)	84 (100%)	87 (100%)	–	229 (100%)	223 (99.6%)	–	–
BMI, kg/m^2, mean (SD)	29.7 (4.4)	30.0 (4.2)	0.66	29.0 (4.5)	28.8 (4.0)	0.65	0.0098
Prior MI, n (%)	37 (44.0%)	36 (41.4%)	0.72	85 (37.1%)	76 (33.9%)	0.48	0.0099
Previous Revascularization, n (%)	25 (29.8%)	20 (23.0%)	0.31	72 (31.4%)	46 (20.5%)	0.008	0.95
Cerebrovascular disease n (%)	11 (13.1%)	3 (3.4%)	0.02	7 (3.1%)	3 (1.3%)	0.21	0.0005
Peripheral vascular disease, n (%)	8 (9.5%)	5 (5.7%)	0.35	11 (4.8%)	18 (8.0%)	0.16	0.59
Risk factors, n (%)							
Hypertension	80 (95.2%)	84 (96.6%)	0.66	191 (83.4%)	190 (84.8%)	0.68	<0.0001
Hyperlipidemia	30 (35.7%)	28 (32.2%)	0.63	90 (39.3%)	81 (36.2%)	0.49	0.38
Metabolic syndrome	77 (91.7%)	78 (89.7%)	0.65	164 (71.6%)	149 (66.5%)	0.24	<0.0001
Current smoker	14 (16.7%)	15 (17.2%)	0.92	59 (25.8%)	53 (23.7%)	0.60	0.04
Qualifying event, n (%)							
UA	17 (20.2%)	24 (27.6%)	0.51	50 (21.8%)	56 (25.0%)	0.72	0.41
NSTEMI	28 (33.3%)	25 (28.7%)	–	86 (37.6%)	79 (35.3%)	0.72	–
STEMI	39 (46.4%)	38 (43.7%)	–	93 (40.6%)	89 (39.7%)	0.72	–
Background medication, n (%)							
Aspirin	82 (97.6%)	84 (96.6%)	0.68	224 (97.8%)	209 (93.3%)	0.02	0.40
ß-blockers	73 (86.9%)	76 (87.4%)	0.93	190 (83.0%)	187 (83.5%)	0.88	0.23
ACEI	73 (86.9%)	77 (88.5%)	0.75	196 (85.6%)	177 (79.0%)	0.07	0.10
Lipid modifying	11 (13.1%)	7 (8.0%)	0.28	25 (10.9%)	17 (7.6%)	0.22	0.64
Diabetes drugs, n (%)							
Insulin	20 (23.8%)	19 (21.8%)	0.76	N/A	N/A		
Sulphonylurea	29 (34.5%)	22 (25.3%)	0.19	N/A	N/A		
Metformin	5 (6.0%)	7 (8.0%)	0.59	N/A	N/A		
TZD	1 (0.01%)	0 (0.0%)		N/A	N/A		

SD standard deviation, *BMI* body mass index, *UA* unstable angina, *NSTEMI* non-ST elevation myocardial infarction, *STEMI* ST elevation myocardial ischemia, *ACEI* angiotensin converting enzyme inhibitor, *TZD* thiazolidinedione, *N/A* not applicable

Comparisons were made using either a two-sample t-test (continuous variables) or chi-square test (non-continuous variables)

The p-values for gender compares the whole group which is a binary variable either male or female

The p-value for qualifying event compares the whole distribution

of FRANCIS was the change in LDL cholesterol after 8 weeks of therapy. All patients provided written informed consent and the study protocol was approved by local and national ethics committees.

hs-CRP levels (Quest Diagnostics, Van Nuys, CA USA), $sPLA_2$-IIA concentration (Cayman Chemical, Ann Arbor, Michigan, USA with modification by CLASS Laboratories, University of Michigan, Ann Arbor, Michigan, USA), and IL-6 levels (R&D Systems, Inc., Minneapolis, MN, USA) were measured as described previously [17].

Statistical analyses

Due to non-normality, changes in $sPLA_2$-IIA, hs-CRP, and IL-6 concentrations were analyzed on natural log-transformed data using an ANCOVA model with baseline value as a covariate and factors for treatment group and country. The dependent variable was the difference of the logarithm of the follow-up value and the logarithm of the baseline value.

For each of the inflammatory biomarkers ($sPLA_2$-IIA, hs-CRP, and IL-6), baseline values were split into groups above and below the median. A logistic regression model was then fitted for each of these 3 two-level variables using a stepwise selection procedure from the following variables: diabetes, age, gender, type of index event (unstable angina/STEMI versus STEMI), body mass index, country, baseline LDL cholesterol level, baseline triglyceride level, history of hypertension, MI, angina, metabolic syndrome, hyperlipidemia, and smoking status (current versus former/never).

SAS software version 9.1.3 (SAS Institute, Inc., Cary, NC, USA) was used to perform the data analysis.

Results

Of the 624 patients enrolled in the trial who received study drug, 171 (27.4%) had diabetes at baseline. The clinical features of patients with and without diabetes in the varespladib methyl and placebo groups are listed in Table 1. Patients with diabetes, compared to those without, were slightly older and more likely to be female; they were more likely to have hypertension and the metabolic syndrome.

As shown in Table 2, patients with diabetes had higher baseline median levels of $sPLA_2$-IIA (306 pmol/L (IQR: 249) vs. 231 pmol/L (IQR: 196), $p=0.0066$), IL-6 (6.03 ng/L (11.69) vs. 4.79 ng/L (7.70), $p=0.009$), hs-CRP (10.2 mg/L (40.2) vs. 8.0 mg/L (24.9), $p=0.0155$). In a multivariate model, the presence of diabetes was a statistically independent predictor of baseline $sPLA_2$-IIA level ($p=0.019$) and IL-6 level ($p=0.011$), and of borderline statistical significance as a predictor of hs-CRP level ($p=0.055$).

The effects of varespladib methyl compared to placebo on levels of $sPLA_2$, hs-CRP, and IL-6 from baseline to the end of treatment at 24 weeks are shown in Figs. 1, 2, and 3, respectively. By 2 weeks, $sPLA_2$-IIA levels were reduced by 80-85% in varespladib methyl-treated patients either with or without diabetes, and these differences persisted throughout the trial (Fig. 1). At 8 weeks of treatment (primary endpoint), varespladib methyl treatment reduced median $sPLA_2$-IIA levels by −83.6% in diabetic patients and by −82.4% in non-diabetic patients; these changes were not statistically different ($p=0.33$).

Among patients with diabetes, hs-CRP levels decreased more with varespladib methyl treatment compared to placebo at 2 (−58.8% vs. −11.0%, $p=0.0004$), 4 (−83.0%

Table 2 Biomarkers at randomization

Variable	Diabetes group Varespladib methyl 500 mg + Atorvastatin 80 mg	Diabetes group Placebo + Atorvastatin 80 mg	Diabetes group Overall	Non-diabetes group Varespladib methyl 500 mg + Atorvastatin 80 mg	Non-diabetes group Placebo + Atorvastatin 80 mg	Overall	Diabetics vs. non-diabetics
Glucose mmol/L (SD)	9.48 (3.57)	8.81 (2.53)	9.13 (3.09)	5.46 (0.72)	5.48 (0.81)	5.47 (0.77)	$p<0.0001$
$HbA1_c$ % (SD)	7.8 (1.7)	7.2 (1.3)	7.5 (1.6)	5.6 (0.3)	5.6 (0.6)	5.6 (0.5)	$p<0.001$
$sPLA_2$-IIA pmol/L (IQR)	243 (199)	339 (438)	306 (249)	232 (216)	229 (190)	231 (196)	$p=0.0066$
hs-CRP mg/L (IQR)	13.0 (44.7)	9.1 (35.2)	10.2 (40.2)	7.0 (21.0)	8.7 (26.6)	8.0 (24.9)	$p=0.0155$
IL-6 ng/L (IQR)	5.89 (11.67)	6.13 (11.28)	6.03 (11.69)	4.79 (7.92)	4.76 (7.76)	4.79 (7.70)	$p=0.009$
LDL-C mmol/L (SD)	3.29 (1.05)	3.28 (0.99)	3.29 (1.01)	3.43 (1.01)	3.39 (1.08)	3.41 (1.05)	$p=0.22$
Troponin I, μg/L (IQR)	2.0 (4.88)	2.0 (4.94)	2.00 (4.94)	2.00 (8.04)	1.80 (4.66)	1.90 (6.56)	$p=0.57$

SD standard deviation, *HbA1c* hemoglobin A1C, *$sPLA_2$-IIA* secretory phospholipase A_2 groups IIA, *hs-CRP* high sensitivity C-reactive protein, *IL-6* interleukin-6, *LDL-C* low-density lipoprotein cholesterol

Data are expressed as means (SD) for glucose, HbA1c and LDL-C. All other data are presented as medians with interquartile ranges

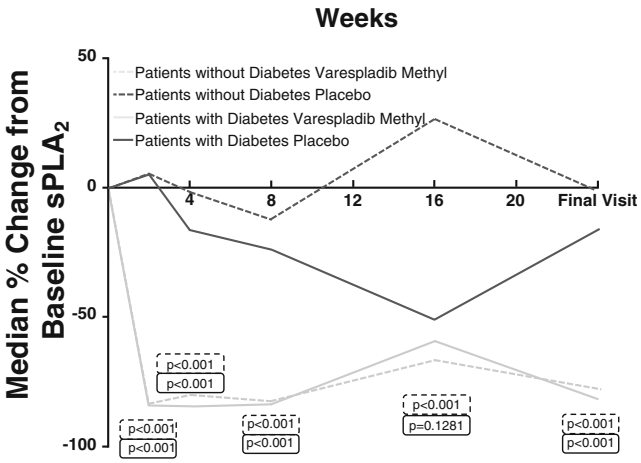

Fig. 1 Effects of varespladib methyl 500 mg daily and placebo on concentrations of secretory phospholipase A_2 groups IIA ($sPLA_2$-IIA) at various times in the trial. The p-values represent differences in $sPLA_2$-IIA concentrations between diabetic and non-diabetic subgroups who were treated with either placebo (solid lines) or varespladib methyl (dashed lines)

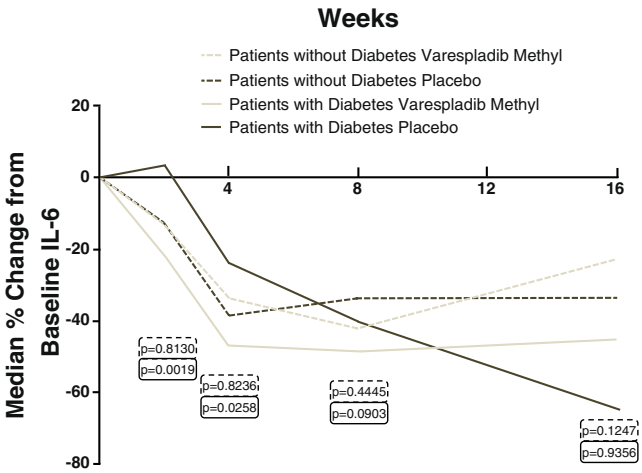

Fig. 3 Effects of varespladib methyl 500 mg daily and placebo on concentrations of interleukin-6 (IL-6) at various times in the trial. The p-values represent differences in IL-6 concentrations between diabetic and non-diabetic subgroups who were treated with either placebo (solid lines) or varespladib methyl (dashed lines)

vs −51.1%, p=0.0013), 8 (−82.8% vs. −67.6%, p=0.0299), 16 (−83.6% vs. −72.4%, p=0.078), and 24 weeks (−89.5% vs. −76.1%, p=0.031, Fig. 2). In patients without diabetes, varespladib methyl treatment was associated with lower hs-CRP levels only at 16 weeks (−81.1%, vs. −71.1% p=0.012). At 8 weeks (primary endpoint), changes in hs-CRP in varespladib methyl-treated patients with and without diabetes were not statistically different (p=0.57).

Similarly, in diabetic patients, the IL-6 reduction with varespladib methyl compared to placebo was statistically significant at weeks 2 (−21.8% vs. +3.5%, p=0.0019) and 4 (−47.1% vs. −23.9%, p=0.026) but dissipated thereafter (Fig. 3). There was no varespladib methyl effect on IL-6 in patients without diabetes. At 8 weeks, differences in IL-6 levels in varespladib methyl-treated patients with and without diabetes were not statistically different (p=0.97).

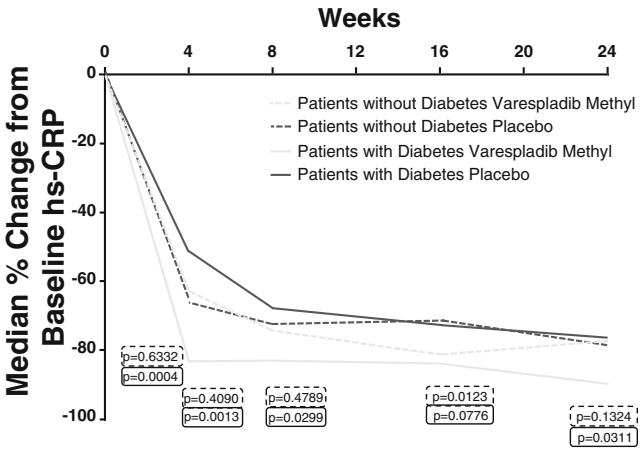

Fig. 2 Effects of varespladib methyl 500 mg daily and placebo on concentrations of hs-CRP at various times in the trial. The p-values represent differences in hs-CRP concentrations between diabetic and non-diabetic subgroups who were treated with either placebo (solid lines) or varespladib methyl (dashed lines)

Associations between baseline glucose values and inflammatory makers were more pronounced in diabetic than non-diabetic patients. In patients with diabetes, the correlations between inflammatory markers and glucose were: $sPLA_2$-IIA r=0.15, p=0.06; hs-CRP r=0.23, p=0.003; and IL-6 r=0.17, p=0.03. In patients without diabetes, the correlations between inflammatory markers and glucose were: $sPLA_2$-IIA r=0.10, p=0.03; hs-CRP r=0.14, p=0.004; and IL-6 r=0.09, p=0.07.

The trial was not powered to detect a significant treatment effect on clinical events. Major adverse cardiovascular events (unstable angina, non-fatal myocardial infarction, non-fatal stroke and death) occurred in 15 of 171 patients with diabetes (8.8%). In patients with diabetes, the overall event rate was 9.5% (8 of 84) in the varespladib–treated patients and 8.0% (7 of 87) in placebo-treated patients. In patients without diabetes, the overall event rate was lower at 7.1% (32 of 453) with a rate of 6.6% (15 of 229) in varespladib-treated patients and 7.6% (17 of 224) in placebo-treated patients.

Among patients with diabetes, treatment-emergent adverse events occurred in 66 (79%) of the varespladib-treated patients and 67 (77%) of the placebo-treated patients as previously reported (17). Corresponding numbers in patients without diabetes were 154 (67%) and 169 (75%). Two patients with diabetes who were treated with varespladib methyl (2.4%) and 4 treated with placebo (4.6%) withdrew due to an adverse event.

Discussion

These results indicate that after an ACS event, patients with diabetes have higher levels of $sPLA_2$-IIA, IL-6, and hs-CRP compared with patients without diabetes. Higher $sPLA_2$ concentration and activity have been linked to worse outcomes after an ACS [11–16], and the risk associated with an elevated IL-6 concentration (>10 ng/mL) was even higher in patients with diabetes [7].

The risk of a recurrent event is highest in the early period post-ACS, but declines over the ensuing weeks in parallel with the decline in CRP levels [18–21]. In the Myocardial Ischemia Reduction with Acute Cholesterol Lowering (MIRACL) trial [16], neither baseline $sPLA_2$-IIA concentration nor $sPLA_2$ activity was associated with recurrent cardiovascular events. However, treatment-related reductions in $sPLA_2$ concentration and activity were significantly less in subjects who had an ischemic event compared to those who did not have an event.

$sPLA_2$ isoenzymes are expressed in arterial smooth muscle cells and hepatocytes [9]. The hydrolysis of phospholipids from cell membranes generates arachidonic acid and lysophospholipids that work in association with other bioactive lipids produced from oxidized lipoproteins to activate inflammatory pathways in various cells in the vessel wall such as tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-6, which in turn induce hepatic and myocardial CRP production [22–24].

FRANCIS (NCT00743925) is a recently completed phase 2 trial that was designed to examine the effects of varespladib methyl on inflammatory biomarkers in 624 patients with ACS who were treated with atorvastatin 80 mg daily [17]. Overall, treatment with varespladib methyl 500 mg daily was accompanied by significant reductions in levels of the inflammatory biomarkers $sPLA_2$-IIA and hs-CRP but not with a statistically significant reduction in IL-6. In this analysis of FRANCIS patients with diabetes, treatment with varespladib methyl, an inhibitor of groups IIA, V, and X $sPLA_2$ isoenzymes suppressed elevated levels of $sPLA_2$-IIA, IL-6 and hs-CRP throughout the follow-up period. As compared with IL-6, changes in hs-CRP with varespladib methyl treatment showed a more treatment consistent effect in the diabetic group, which is probably due to less analytical variability of this measure [25]. For these reasons, hs-CRP has been considered a more useful biomarker of inflammatory activity. Although we postulated an enhanced anti-inflammatory response to varespladib methyl in ACS patients with diabetes, 8-week differences in these biomarkers were not statistically different from non-diabetes patients.

Consistent with established associations between glycemic status and transcriptional activation of inflammatory pathways in the arterial wall of patients with diabetes [1, 4, 26], we report higher correlations between baseline glucose concentrations and the inflammatory markers in patients with diabetes than in patients without diabetes.

Conclusions

Varespladib methyl significantly reduced the post-ACS inflammatory response in patients with and without diabetes [17]; however, this subgroup analysis indicates that the anti-inflammatory effect was limited to patients with diabetes. Further corroboration of the differences in the anti-inflammatory effects of varespladib methyl in diabetic and non-diabetic patients requires further investigation in the larger VISTA-16 trial [27].

The association between glycemic status and inflammation is consistent with established pathways documenting increased transcriptional pro-inflammatory activation in patients with poorly controlled diabetes. Thus, it might be anticipated that the anti-inflammatory effect of $sPLA_2$ inhibition might be greater in patients with more advanced and poorly controlled diabetes. Although we did not demonstrate larger changes in circulating inflammatory biomarkers with varespladib methyl treatment, this trial does not preclude the possibility of a larger anti-inflammatory effect in the vessel wall of patients with diabetes. The potential effects of these biomarker changes in varespladib methyl-treated ACS patients with diabetes will require investigation in an event-driven clinical trial.

Conflicts of interest Drs. Fraser and Hislop are employees of Anthera Pharmaceuticals and they have ownership interest in Anthera Pharmaceuticals.

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