Decreased CRP levels in response to a six-week, once-daily oral insulin regimen

Roy Eldor[1], Miriam Kidron[2], Yanitsa Miteva[3], Ehud Arbit[2]

[1] Hadassah Medical Center, Diabetes and Endocrinology Units, Jerusalem, Israel

[2]Oramed Pharmaceuticals, Jerusalem, Israel [3]Aenova, Kirchberg, Switzerland

81st EAS Congress
June 2-5, 2013 | Lyon, France

Introduction

Elevated c-reactive protein (CRP) levels, a marker of inflammation, have been associated with increased risk for cardiovascular disease (CVD) in Type 2 diabetes mellitus (T2DM). Some researchers have even suggested that CRP can act as a predictor of T2DM, where chronic inflammation induces metabolic sequelae related to the pathophysiology of diabetes. Thus, a multitarget treatment regimen effectively managing T2DM while simultaneously reducing inflammation and preventing CVD, would be of great benefit to the steadily growing diabetes population. Although hyperinsulinemia and diabetes are regarded as pro-inflammatory conditions, growing evidence suggests that insulin itself may have an anti-inflammatory effect.

Objective: To assess the impact of a six-week administration of the ORMD-0801 oral insulin formulation on serum CRP concentrations in T2DM patients.

Study Design: This was a multi-site (n=5), placebo-controlled, randomized, double-blind, study, in which 21 T2DM subjects received a daily insulin-based treatment (8 mg/capsule, 2 capsules/day) for a period of six weeks, while 8 received placebo. Both capsules were orally administered at bedtime.

Methods: Blood samples were drawn from fasting subjects at the start and at the end of the six-week treatment period, for determination of plasma CRP and insulin concentrations. Pretreatment and posttreatment marker concentrations were compared.

Patient Demographics: No significant differences in baseline patient demographics were noted between the two treatment groups (Table 1). The majority of treated patients were obese and were battling T2DM for over four years.

Table 1. Patient Demographics

	Treatment Group			Treatment Group	
	Oral Insulin (N=21)	Placebo (N=8)		Oral Insulin (N=21)	Placebo (N=8)
Age (years)			CRP (mg/L)		
Mean (SD)	50.33(11.18)	54.13(11.05)	Mean (SD)	6.98 (6.6)	3.21 (3.1)
Min, Max	21, 63	30, 66	Min, Max	1.3, 27.7	0.8, 9.4
Sex, n (%)			WHO BMI classification, n (BMI mg/m^2)		
Male	9 (42.9)	6 (59.3)	Normal	3 (14.3)	1 (12.5)
Female	12 (57.1)	2 (25.0)	Overweight	7 (33.3)	3 (37.5)
			Obese	11 (52.4)	4 (50.0)
Baseline Weight (kg)			Duration of T2DM (years)		
Mean (SD)	81.8 (14.50)	83.2 (14.02)	Mean (SD)	5.0 (3.4)	4.1 (3.4)
Min, Max	61.3, 112.0	60.0, 104.3	Min, Max	0.5, 11.1	0.4, 10.9
HbA1c (%)					
Mean (SD)	8.6 (1.0)	8.3 (1.0)			
Min, Max	7.3, 10.4	7.2, 9.7			

Results

A six-week regimen of ORMD-0801 induced significant decreases in morning plasma insulin levels (-0.82 ±2.48 mU/L) in the insulin-treated cohort, in contrast to the increase (1.58 ±2.52 mU/L) observed in the placebo-treated group (Figure 1A, p=0.031)). Insulin responses were observed among 40% of the ORMD-0801-treated cohort, two-fold more than the incidence among placebo-treated patients (Figure 1B). In parallel, morning CRP levels dropped by a mean -0.22 mg/L in insulin-treated patients, versus a mean 3.05 mg/L rise measured among placebo-treated patients (Figure 1A, p=0.042). The homeostatic model assessment (HOMA) index (a measure of hepatic insulin resistance) showed a clear trend of decrease among ORMD-0801-treated patients in contrast to an increase in the placebo group (T-test p=0.07 and by non-parametric Median test p=0.07) CRP responses were noted among 25% of the oral insulin-treated patients, while all placebo-treated patients failed to respond (Figure 1B). Two cases of hypoglycemia were recorded in ORMD-0801-treated patient diaries, both of which were mild and fully resolved upon juice consumption. In addition, four mild adverse events were reported in this same cohort, and were all seemingly unrelated to study treatment.

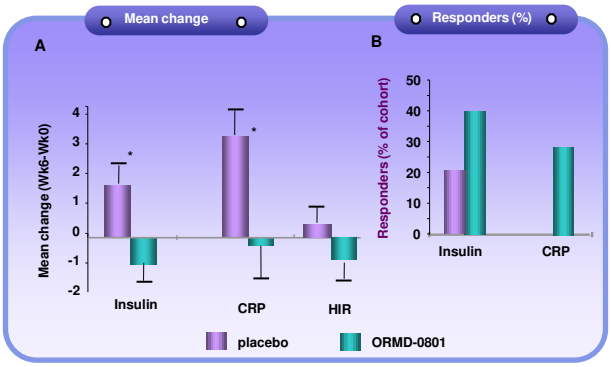

Figure 1. Serum insulin and CRP responses to oral insulin. T2DM patients were treated once daily with either two 8 mg insulin ORMD-0801 (n=21) or with placebo (n=8) capsules. Blood samples drawn at the start of the study and after a 6-week treatment period were tested for marker levels. A. Mean changes (±SD) in plasma insulin (p=0.031) and CRP levels (p=0.042) and hepatic insulin resistance (HIR) between the samples of day 0 and samples taken after the 6-wk treatment period. B. Subjects demonstrating a ≥10% blood marker concentration decrease from baseline were considered responders for that specific marker.

Discussion and Conclusions

Hepatic insulin resistance (HIR) is considered a major trigger of dysglycemia, including fasting and post-prandial hyperglycemia. Animal studies and models of hepatic dysfunction (e.g. hepatic cirrhosis) provide strong support that peripheral insulin resistance and proinflammatory states are secondary to hepatic fat deposition which, in turn, begets a local inflammatory process. Furthermore, the combined consequence of hyperglycemia, dyslipidemia, and increased circulating adipokines and proinflammatory cytokines are known to promote hepatic production of CRP. Apart from the gradual rectification of insulin profiles, the present findings demonstrate a possible impact of ORMD-0801 on chronic inflammatory states. Further studies will be required to assess whether ORMD-0801 treatment translates to reduced risk of CVD-related morbidity and mortality in T2DM patients.

oramed Pharmaceuticals Inc

www.oramed.com

Correspondence: Dr. Miriam Kidron miriam@oramed.com Tel: +972-2-566-0001

Acknowledgments : The authors would like to thank Dr. Yehudit Posen for her technical assistance.