

Diabetes Close Up's 2004 ADA Selected Five-Star Abstracts

1. Glucose Excursions Detected by the Continuous Glucose Monitoring System and Missed by Routine Self-Monitoring Blood Glucose Measurements in Patients with Type 1 and Type 2 Diabetes Requiring Insulin

Abstract Number: 444-P

Authors: SCOTT W. LEE, MARIANA FREITAS, JERROLD PETROFSKY, EDWARD CHAO, LOURDES GOMEZ, RICHARD IM, RICHARD MAGBUAL

Institution: CA

Results: The Continuous Glucose Monitoring System (CGMS) otherwise known as the glucose sensor provides a continuous integrated picture of an individual's glycemic profile over a 72 hour period. This study was conducted to determine the incidence of hypoglycemia and hyperglycemia detected by CGMS but missed by routine self-monitoring blood glucose (SMBG). A secondary aim was to understand whether the CGMS would identify patterns of glucose excursions that resulted in changes to diabetes management.

Retrospective data collection was performed on 24 individuals who were insulin requiring and consecutively utilized CGMS as part of routine standard of care. Patient characteristics included: type 1 diabetes (n = 8) and type 2 diabetes (n = 16), 50% female, 25% using CSII, age 42 ± 14 years, duration of diabetes 17 ± 11 years. The 24 patients had an average of 13.8 ± 6.6 paired sensor/meter readings with a 0.8 ± 0.2 correlation coefficient; $15.2 \pm 7.1\%$ mean absolute difference compared to SMBG.

In every (100%) individual who performed CGMS, there were either hypoglycemic or hyperglycemic excursion(s) which were undetected by SMBG. Stratified analysis of data revealed: hyper- or hypoglycemia during the night in 96% of patients, 96% of patients had hyperglycemia not detected by SMBG and/or 63 % of patients had hypoglycemia not detected by SMBG. In all patients, there were changes in management based on the CGMS tracings: 92 % had some form of medication change which included insulin adjustments, 46% had a dietary prescription change, 17% had a lifestyle recommendation and/or 25% had a referral.

CGMS provided clinically useful information on hyper- hypoglycemic excursions that were missed by routine SMBG (especially during the night). Patterns observed with CGMS resulted in changes to diabetes management plans in every patient observed.

Category: Clinical Therapeutics/New Technology

DCU Comment: This is a very interesting study, though we would have liked to have seen a significantly larger patient cohort. While some have suggested that patients can adequately self-monitor with current testing systems, we believe that the glucose excursions highlighted by this article make a strong case for continuous monitoring. Glucose excursions are a hallmark of the disease and those who can better control them will enjoy greater long-term health.

2. Clinical Utility of the FreeStyle Navigator™ Continuous Glucose Monitor

Abstract Number: 1921-PO

Authors: BRUCE W. BODE, BEN FELDMAN

Institution: Atlanta, GA; Alameda, CA

Results: The TheraSense FreeStyle Navigator™ continuous glucose monitor consists of a subcutaneous electrochemical sensor inserted for three days, and wirelessly coupled to a handheld meter/information display. User studies with this system were recently completed with a total of 102 subjects (61 Type 1 and 41 Type 2) at seven clinical sites. Sensors were self-inserted, and the system was self-calibrated via arm-stick blood glucose measurements at 1, 3 and 24 hours post insertion. Error Grid Analysis (using finger-stick capillary blood glucose values as the reference) of 9160 data pairs gave 74.7% of readings in region A, and 96.5% in either region A or B. Alarm accuracy was also evaluated: the hyperglycemic alarm

(threshold = 70 mg/dL) provided a sensitivity of 63.2% and a positive predictive value (PPV) of 59.5%. The hyperglycemic alarm (threshold = 250 mg/dL) provided a sensitivity of 68.7% and a PPV of 78.4%. In addition to static glucose concentration measurements, the system provides valuable glucose trend information, based on one-minute updated values, through both (1) a 5-position trend arrow, and (2) projected (future) glucose alarms with a user-chosen sensitivity. The features provide the potential to anticipate, minimize, and even avoid undesirable glycaemic excursions. The presentation will focus on the clinical utility of real-time Navigator™ data traces, with numerous examples drawn from real-life continuous data.

Category: Clinical Therapeutics/New Technology

DCU Comment: This data continues to support the notion that the FreeStyle Navigator will be a valuable diagnostic tool for day-to-day management of diabetes; we found the overall EGA score of 96.5% particularly compelling. We note that accuracy of the alarm functions has been a challenge for meters to date and we hope they will continue to improve over time – the Navigator alarm results show substantial improvement to current offerings. We believe that this data is sufficient to make the Navigator a strong product offering and we believe further studies will show that the trending analysis offered by the system can go a long way toward helping those with diabetes better control their disease.

3. Reduced Exposure to Hyperglycemia and Decreased Risk of Hypoglycemic Events in Patients with Type 1 Diabetes Using a Long-Term Continuous Glucose Sensor Abstract Information

Abstract Number: 5-LB

Authors: RUSSELL SCOTT, ZARNIA MORRISON, SATISH GARG

Institution: Christchurch, New Zealand; Denver, CO

Results: A second generation implantable glucose sensor (DexCom Inc.) was implanted in 10 patients with Type 1 diabetes. The patients were implanted for 127 ± 3 days, during which they were first blinded to the data (62 ± 6 days) and then unblinded (65 ± 7 days). Of 1620 paired sensor/blood glucose meter points, > 90% fell within the A&B regions of the Clarke Error Grid. Hyper and hypoglycemic excursions were defined as sensor glucose values persisting for at least one hour > 200 mg/dl or < 80 mg/dl (alert settings). Glucose excursion frequency did not change when comparing blinded to unblinded (1.36 ± 0.23 vs. 1.48 ± 0.33 excursions/day hyper, and 1.32 ± 0.23 vs. 1.32 ± 0.26 excursions/day hypo). However, mean hyperglycemic and hypoglycemic excursion durations were significantly reduced by 92 minutes and 43 minutes respectively (Table). In addition, the mean amplitude of the hyperglycemic excursion was reduced by 20 mg/dl, whereas the mean amplitude below 80 mg/dl was unchanged. When expressed in terms of exposure to hyperglycemia (product of amplitude and duration), a 40% reduction occurred after unblinding (Table).

These results demonstrate that patients using the sensor with alerts were able to significantly reduce the time and amplitude of their excursions above 200 and time (but not amplitude) below 80. We conclude that using a continuous glucose sensor reduces glucose excursions enables patients to improve their overall glycaemic control.[table1]

Category: Clinical Therapeutics/New Technology

DCU Comment: Glucose excursions are very damaging to those with diabetes – while hyperglycemia damages the tissues, hypoglycemia can lead to coma and death. Proper disease management means controlling these excursions as much as possible. This study helps support the notion that continuous monitoring can help people shorten these excursions and reduce their severity. While longer-term data will no doubt be key in convincing the clinical community, this abstract is compelling in its own right – demonstrating in a very small sample set that continuous monitoring can help moderate glucose levels.

4. Glucose Excursions Detected by the Continuous Glucose Monitoring System and Missed by Routine Self-Monitoring Blood Glucose Measurements in Patients with Type 1 and Type 2 Diabetes Requiring Insulin

Abstract Number: 444-P

Authors: SCOTT W. LEE, MARIANA FREITAS, JERROLD PETROFSKY, EDWARD CHAO, LOURDES GOMEZ, RICHARD IM, RICHARD MAGBUAL

Institution: CA

Results: The Continuous Glucose Monitoring System (CGMS) otherwise known as the glucose sensor provides a continuous integrated picture of an individual's glycemic profile over a 72 hour period. This study was conducted to determine the incidence of hypoglycemia and hyperglycemia detected by CGMS but missed by routine self-monitoring blood glucose (SMBG). A secondary aim was to understand whether the CGMS would identify patterns of glucose excursions that resulted in changes to diabetes management.

Retrospective data collection was performed on 24 individuals who were insulin requiring and consecutively utilized CGMS as part of routine standard of care. Patient characteristics included: type 1 diabetes (n = 8) and type 2 diabetes (n = 16), 50% female, 25% using CSII, age 42 ± 14 years, duration of diabetes 17 ± 11 years. The 24 patients had an average of 13.8 ± 6.6 paired sensor/meter readings with a 0.8 ± 0.2 correlation coefficient; $15.2 \pm 7.1\%$ mean absolute difference compared to SMBG.

In every (100%) individual who performed CGMS, there were either hypoglycemic or hyperglycemic excursion(s) which were undetected by SMBG. Stratified analysis of data revealed: hyper- or hypoglycemia during the night in 96% of patients, 96% of patients had hyperglycemia not detected by SMBG and/or 63 % of patients had hypoglycemia not detected by SMBG. In all patients, there were changes in management based on the CGMS tracings: 92 % had some form of medication change which included insulin adjustments, 46% had a dietary prescription change, 17% had a lifestyle recommendation and/or 25% had a referral.

CGMS provided clinically useful information on hyper- hypoglycemic excursions that were missed by routine SMBG (especially during the night). Patterns observed with CGMS resulted in changes to diabetes management plans in every patient observed.

Category: Clinical Therapeutics/New Technology

DCU Comment: We believe this study is a strong affirmation of the utility of continuous monitoring. The fact that 100% of those in the study experienced excursions that were missed by self-monitoring shows powerfully that continuous testing can do things that traditional testing cannot. Importantly, almost 2/3 of those in the study had hypoglycemic events that would not have been recognized with continuous monitoring. What's more, almost all patients had a change in their medicine due to the results of the continuous monitoring and almost half changed their diets.

5. Patient Satisfaction with Continuous Glucose Monitoring Devices: Direct Comparison of MiniMed CGMS and Cygnus GlucoWatch

Abstract Number: 1934-PO

Authors: KALPANA KAUSHAL, LOUISE M. WONG, HEATHER J. RAMSBOTTOM, ROBERT J. YOUNG, JOHN M. GIBSON

Institution: Manchester, United Kingdom

Results: Optimisation of glycemic control is essential in pregnancy to improve clinical outcome. In a randomised crossover trial we assessed the acceptability of the MiniMed CGMS [MM] and Cygnus GlucoWatch [GW] in a cohort of women with diabetes who were either pregnant or attending pre-pregnancy counselling. Devices were used in random order (MM for 72h, GW for 3 12h periods) with instruction and debriefing by the same healthcare professional. A 29-part questionnaire was administered after each device to obtain specific feedback. Questionnaire responses were based on a seven-point Likert scale. Fourteen women (age $33 \pm 6.1y$; diabetes duration $14.4y \pm 9.7y$) completed the study. Using scores

of 5 or 6 on the Likert scale to represent a strongly positive perception; 93% (MM) vs 21% (GW) found the device easy to use; 64% (MM) vs 1% (GW) felt no discomfort; 64% (MM) vs 0% (GW) had no skin reaction, and; 82% (MM) vs 46% (GW) perceived no problems at work. The MM became disconnected in 21% but functioned well in 79%. The GW had more technical problems; in 71% it failed to record for at least 1 time period. With both devices, 36% experienced no interference with normal daytime activity, and 50% (MM) vs 43% (GW) felt no self-consciousness during use. The overall score strongly favoured the MM (73.8 ± 11.2 vs 62 ± 14.1 , $p=0.008$), particularly for items relating to practicalities of use (MM $[41.6 \pm 6.3]$ vs GW $[31.2 \pm 7.3]$; $p<0.001$). Interestingly 64% gained a better understanding of blood glucose variation using GW vs 43% with MM, but there was no difference between the devices in the overall score for change in understanding and management of diabetes (MM 22.1 ± 5.3 vs GW 22.8 ± 4.5 ; $p=NS$). Use of either device resulted in insulin dose/type changes in 86% of women with a consequent significant improvement in glycemic control (baseline HbA1c $8.0 \pm 1.4\%$ vs $7.4 \pm 1.2\%$, $p=0.016$). Whilst the MM was the preferred device, particularly from the ease of use standpoint, most women felt GW gave them a better understanding of glucose fluctuation.
Category: Clinical Therapeutics/New Technology

DCU Comment: This study is interesting on several levels. First of all, it maintains that a number of patients found the GlucoWatch device hard to use, uncomfortable, and unreliable. What's interesting, though, is that many patients believed that the GlucoWatch provided them with a better understanding of their glucose variance, suggesting that patients are looking for something beyond intermittent testing and even first generation devices with technical issues showed key value to patients. This abstract advances our belief that continuous sensing devices are well within the capabilities of the average person and can provide valuable information without any lifestyle compromises.

6. Thiazolidinediones Improve Beta-Cell Function in Type 2 Diabetic Patients Abstract Information

Abstract Number: 11-LB

Authors: AMALIA GASTALDELLI, ANDREA MARI, YOSHINORI MIYAZAKI, MASAFUMI MATSUDA, ELE FERRANNINI, RALPH A. DEFRONZO

Institution: San Antonio, TX; Pisa, Italy; Padova, Italy

Results: Thiazolidinediones (TZDs) improve glycemic control and insulin sensitivity in patients with type 2 diabetes mellitus (T2DM). There is growing evidence in animal and in vitro studies showing that TZDs improve pancreatic B-cell function. The aim of this study was to determine whether the TZD-induced improvement in glycemic control is associated with improvement in pancreatic B-cell function. 30 T2DM patients (age= 53 ± 2 yr; BMI= 29.4 ± 0.8 kg/m²; fasting plasma glucose [FPG]= 10.3 ± 0.4 mM; HbA1c= 8.2 ± 0.3 %) were randomized to 4-months of treatment with a thiazolidinedione (TZD): pioglitazone (PIO, n=9), rosiglitazone (ROSI, n=10) or placebo (Plc, n=10). All subjects received a 75g OGTT with determination of glucose, insulin and C-peptide conc. every 15 min for 2h. Before and after TZD treatment, insulin secretion was evaluated by deconvolution of C-peptide data and insulin sensitivity by the 2-step euglycemic insulin (40 and 160 mU \times m⁻² \times min⁻¹) clamp with [3-³H]glucose. TZD improved fasting glucose (Δ FPG -1.3 ± 0.4 [PIO], -2.8 ± 0.6 [ROSI] vs 0.8 ± 0.4 [Plc] mmol/l), mean glucose during the OGTT (Δ AUC-G -0.20 ± 0.08 [PIO], -0.43 ± 0.07 [ROSI] vs 0.11 ± 0.08 [Plc] mol/l), insulin-mediated total-body glucose disposal (Δ TGD step1, 8.3 ± 3.2 [PIO], 1.7 ± 1.8 [ROSI] vs 0.1 ± 1.3 [Plc] and Δ TGD step2, 15.7 ± 3.9 [PIO], 15.2 ± 4.0 [ROSI] vs -3.8 ± 3.1 [Plc] mmol \times kg⁻¹ \times min⁻¹) and decreased mean FFA during the OGTT (Δ AUC-FFA -8.0 ± 6.9 [PIO], -16.8 ± 4.7 [ROSI] vs 11.0 ± 7.5 [Plc] mEq/l) (all $p<0.01$, by ANOVA).

The insulin secretory response to the glucose load was significantly improved in both TZD-treated groups (Δ ISR/ Δ AUC-glucose 13.8 ± 5.8 [PIO], 12.1 ± 4.8 [ROSI] vs -1.8 ± 4.1 [Plc] nmol/l, $p<0.04$ Plc vs TZD) and this increase was correlated with the improvement in TGD as measured during 160 mU clamp ($r=0.39$, $p<0.03$) and inversely to the improved suppression of FFA during OGTT ($r=0.41$, $p<0.03$).

CONCLUSION: In T2DM patients, TZD treatment induces recovery of pancreatic B-cell function, probably mediated by the reduction in plasma FFA and FFA metabolites within the B-cell.

Category: Clinical Therapeutics/New Technology

DCU Comment: This is an intriguing study. While it's certainly not news that TZD improves glucose control, the notion that TZD improves beta-cell function is a more novel concept. If these results are duplicated in additional (and larger) studies, then the case for prescribing TZD's as part of standard T2DM drug therapy will only strengthen.

7. Rosiglitazone Plus Metformin Combination Effects on CV Risk Markers Suggest Potential CV Benefits in Type 2 Diabetic Patients

Abstract Information Presented during: Dyslipidemia, the Metabolic Syndrome, and Cardiac Disease - 06/05/2004 (02:45 - 04:45 PM) Abstract Number: 121-OR

Authors: PETER N. WEISSMAN, BARRY J. GOLDSTEIN, JOHN C. CAMPBELL, ERROL M. GOULD, BRIAN R. WATERHOUSE, LEANNE J. STROW, ALEXANDER R. COBITZ Institution: Miami, FL; Philadelphia, PA; King of Prussia, PA

Results: Insulin resistance (IR) is associated with increased CV risk. Rosiglitazone (RSG), an insulin sensitizer of the thiazolidinedione (TZD) class, is effective in reducing IR but metformin (MET), a biguanide, has a mechanism of action that is different from TZDs and has inconsistently demonstrated insulin sensitizing properties. In this sub-study, type 2 diabetic subjects received open-label MET (500 mg bd) for at least three weeks and then were randomized in blinded fashion to receive combination treatment with added RSG (2 mg bd, n = 70) or an additional 500 mg MET (1500 mg/d, n = 57). After 8 weeks, the doses were titrated to a total daily dose of 8 mg + 1 g (RSG + MET) and 2 g (MET) for a further 16 weeks. Treatment with RSG + MET resulted in significant and favorable effects on known markers of CVD risk beyond that of MET monotherapy. Furthermore, these results were not attributed to differences in HbA_{1c} between the two groups and suggest that combination treatment with these two common oral anti-diabetic agents may provide complementary and additive CV benefits in type 2 diabetes patients.[table1] Category: Complications, Macrovascular

DCU Comment: Studies like this one help to support the case for PPAR agonists. Given the accumulating data on the role of PPARs in lipid chemistry and atherosclerosis, this study is quite encouraging. Cardiovascular disease is the major lethal co-morbidity of diabetes and any drug compound that can help glucose control and reduce cardiovascular disease is a great win-win proposition.

8. Beneficial Effects of Thiazolidinediones on Myocardial Infarction Risk in Patients with Type 2 Diabetes Abstract Information

Abstract Number: 1009-P

Authors: CAROL E. KORO, QINGGONG FU, RIAD G. DIRANI, DONALD O. FEDDER Institution: Upper Providence, PA; Baltimore, MD

Results: Type 2 diabetes is associated with increased cardiovascular risk. Thiazolidinediones (TZDs), effective antidiabetic agents, have been shown to improve insulin sensitivity, enhance endothelial function and reduce mediators of prothrombotic activity and inflammatory markers of cardiovascular risk. A case-control study was conducted to determine whether TZDs alter the risk of myocardial infarction (MI) compared to traditional antidiabetic agents.

Incident cases of MI hospitalizations among type 2 diabetic patients were identified from the Integrated Healthcare Information Services (IHCIS) managed care database from 1997 and 2002. Patients with prior MI were excluded. Six controls were matched to each case on age, gender and calendar year of MI diagnosis (index year). The odds of MI were modeled using conditional logistic regression, adjusting for age, gender, index-year, Nitrate use, ACE inhibitors, Beta-blockers, diuretics, hyperlipidemia and hypertension.

Two hundred and twenty nine incident cases of MI hospitalizations were matched to 1,374 controls. Compared to insulin monotherapy, TZD use was associated with 49% reduction in the risk of MI (95% CI = 0.27-0.95). Among specific TZDs, the adjusted odds ratio for rosiglitazone on MI risk was 0.43 (95% CI = 0.19-0.97) and that for pioglitazone was 0.61 (95% CI = 0.27-1.39).

TZD use is associated with a reduction in MI risk in type 2 diabetes. This potentially translates into economic benefit. Numerous outcomes studies are in progress to prospectively confirm these findings.

Category: Epidemiology

DCU Comment: PPAR agonists like TZD's are already known to be potent actors in lowering blood glucose, but the evidence of deriving cardiovascular benefit as well is very strong data indeed. While evidence of improved lipid modeling or endothelial function is all well and good, this study provides stark and simple end-result information – people who take TZD's are less likely to suffer an MI.

9. Sequence Variation in *PPARG* May Underlie Differential Response to Thiazolidinediones

Abstract Information Abstract Number: 1146-P

Authors: JOHANNA K. WOLFORD, KIMBERLY A. YEATTS, SHARANJEET K. DHANJAL, THOMAS A. BUCHANAN, RICHARD M. WATANABE

Institution: Phoenix, AZ; Los Angeles, CA

Results: Thiazolidinediones (TZD) are agonists for the peroxisome proliferator-activated receptor- γ (PPARG) and constitute a class of insulin-sensitizing drugs used to treat type 2 diabetes (T2D). TZDs have been found to reduce rates of T2D in at-risk subjects, indicating that they may be an effective means of T2D prevention. However, over 30% of TZD-treated subjects do not respond to treatment with an increase in insulin sensitivity. We hypothesized that variation in the *PPARG* gene may play a significant role in mediating TZD-stimulation of PPARG and/or its downstream components. Thus, we screened \approx 20 kb of *PPARG* corresponding to all exons, promoters, and exon/intron boundaries in 82 Latinas with previous gestational diabetes who had participated in the *TRoglitazone In the Prevention Of Diabetes* (TRIPOD) study. Women were non-diabetic when enrolled and non-responders were the 27 women in the lowest tertile of change in minimal model insulin sensitivity (S \square I) during the first 3-months of TZD therapy (median change -0.1 units). We identified and genotyped 17 variants. Of these, four variants, two of which were located in the A2 promoter and two in exons 1 and 6, showed trends for association with TZD response, with an average difference in minor allele frequency of 11.8-14.8% between response groups ($0.02 \leq P \leq 0.07$). Three of these variants were also associated with changes in phenotypes during the first 3 months of TZD treatment (see table). Our results suggest that variation in *PPARG* may account for response to TZD therapy in women at-risk for T2D

DCU Comment: Although this abstract is unlikely to translate into any sort of immediate therapy change, we believe the findings in this study could be very powerful in the long run. How and why certain people fail to respond to drugs is a problem that has vexed clinicians for decades (and probably centuries). By studying the issue at the genetic level, these researchers have offered the insight that genetic variation may be a major factor in response/non-response for TZD therapy. Perhaps this can lead down the road toward upfront genetic testing that would allow doctors to customize therapy for each person – prescribing drugs that will work optimally given a patient's particular genetic variation(s). We hope studies like this will encourage further exploration of the role of genetic variation in diabetes drug response.

10. R483, a Novel TZD Exhibiting Superior PPAR-gamma Activation Compared with Rosiglitazone, Pioglitazone and MCC-555, Lowers Blood Glucose Levels In Vivo

Abstract Number: 648-P

Authors: ANDREAS CHRIST, ASTRIDE SCHNOEBELEN, HANS F. KUEHNLE, MARKUS MEYER

Institution: Basel, Switzerland

Results: Thiazolidinedione (TZD) agonists bind to and activate peroxisome proliferator-activated receptor-gamma (PPAR γ). R483 is a novel TZD currently being developed to target insulin resistance associated with type 2 diabetes. Preclinical studies were performed to analyze the affinity and binding of R483 to PPAR γ . In a radioligand binding assay R483 bound to PPAR γ with an affinity of 0.07 nM. The other TZDs tested bound with significantly lower affinities: 1.09 nM, 10.00 nM and 7.90 nM for rosiglitazone, pioglitazone and MCC-555, respectively. Ligand-mediated transactivation was tested in transiently transfected cells. R483 showed the highest potency for stimulating PPAR γ activity, with an EC $_{50}$ of 0.14 nM, comparable with rosiglitazone (0.41 nM) but several fold higher than that seen with pioglitazone and MCC-555 (1.56 nM and 2.41 nM, respectively). The effect on stimulation of PPAR γ -dependent gene expression was comparable between R483 and rosiglitazone, while pioglitazone and MCC 555 exerted only 43% and 27% of this effect, respectively. As with all the tested TZDs, no relevant activation of PPAR α and Δ receptors were detected. The effect of R483 on glycemia was evaluated in ZDF rats after 11 days of dosing with 10 and 50 mg/kg of R483. A 50% decrease in fasted blood glucose was observed following the 10 mg/kg dose and was further decreased to 68% of controls at 50 mg/kg. Only a minor increase in glycemia was observed following an oral glucose load. In *fa/fa* rats, 1 and 10 mg/kg of R483 significantly decreased serum concentration of insulin (60% and 76%, respectively), triglycerides (66% and 82%, respectively) and free fatty acids (86% and 81%, respectively) versus controls. AUC $_{0-2}$ glucose following an oral glucose tolerance test with 10 mg/kg R483, showed a marked reduction (50%) versus controls. These results indicate that R483 is superior at activating PPAR γ compared with rosiglitazone, pioglitazone and MCC-555, and is able to control hyperglycemia in vivo. Category: Clinical Therapeutics/New Technology

DCU Comment: TZD's are already known to be highly effective drugs. This data suggests that R483 could be even more powerful than those drugs already available. While this study was not powered to compare the compounds from an "end user standpoint", the biochemical data of transactivation and affinity are compelling. Although better affinity and transactivation do not always lead to better in vivo performance, they can point the way to a more effective therapy (and sometimes with lower side-effects). Based on this early data, we would maintain that R483 is certainly a drug that merits attention as it moves through the pipeline.

11. Effect of Exenatide (Exendin-4) on Glycemic Control and Safety over 30 Weeks in Sulfonylurea-Treated Patients with Type 2 Diabetes

Abstract Information Presented during: [Incretin Mimetics - 06/08/2004 \(10:15 - 12:15 PM\)](#)

Abstract Number: 352-OR

Authors: JOHN BUSE, ROBERT HENRY, JENNY HAN, DENNIS D. KIM, MARK FINEMAN, ALAIN D. BARON

Institution: Chapel Hill, NC; San Diego, CA

Results: Exenatide (exendin-4) is an incretin mimetic with potential antidiabetic activity. The aim of this study was to evaluate the effects of exenatide on glycemic control and safety among patients with type 2 diabetes taking at least the maximally effective dose of a sulfonylurea (SFU). This was a triple-blind, placebo (PBO)-controlled, multicenter, 30-week study, with a 4-week, single-blind, placebo lead-in period, after which subjects were randomized to 5 Mg subcutaneous exenatide twice daily (BID; arms A and B) or PBO for 4 weeks. Subsequently, doses in arm A remained at 5 Mg while doses in arm B were escalated to 10 Mg BID. Subjects continued SFU therapy. Of the 377 subjects in the intent-to-treat population (ITT) (60% M, 55 \pm 11 y, BMI 33.4 \pm 5.6 kg/m 2 , A1C 8.6 \pm 1.2%), 260 (69%) completed the study (60% of PBO and 73% of exenatide patients). At Week 30, exenatide treatment resulted in significant mean reductions in A1C from baseline (10 Mg: -0.9 \pm 0.1%, 5 Mg: -0.5 \pm 0.1% vs. PBO: +0.1 \pm 0.1%, P <0.001 for each exenatide arm, ITT). In the evaluable population, 41%, 33%, and 9% of subjects attained an A1C \leq 7% (10 Mg, 5 Mg, and PBO, respectively). The 10 Mg arm had a significant mean reduction in body weight from baseline to Week 30 (10 Mg: -1.6 \pm 0.3 kg vs. PBO: -0.6 \pm 0.3 kg,

$P < 0.05$, ITT). Compared with PBO, HOMA-B increased in both exenatide arms ($P \leq 0.0075$) and a decrease in the proinsulin-to-insulin ratio was observed in the 10 Mg arm ($P = 0.001$). Treatment-emergent adverse events were generally mild-to-moderate, with nausea and hypoglycemia being the most frequent. No severe hypoglycemia occurred. In summary, over 30 weeks, exenatide significantly reduced A1C in patients with type 2 diabetes failing maximally effective doses of SFU. Exenatide was generally well-tolerated, resulted in significant reductions in body weight at the highest dose, and was associated with improved markers of B-cell function.

Category: Clinical Therapeutics/New Technology

DCU Comment: GLP-1 analogs are intriguing as a class in their own right, and exenatide appears to offer significant efficacy in vivo. The side effects shown to date appear manageable and the reduction in HbA1c levels are compelling. If A1C and weight loss are both sustained over longer periods of time, we do not think the injectable nature of the drug will be as major a deterrent as some believe.

12. Effects of Exenatide (Exendin-4) on Glycemic Control and Weight in Patients with Type 2 Diabetes Treated with Metformin and a Sulfonylurea

Abstract Number: 10-LB

Authors: DAVID M. KENDALL, MATTHEW C. RIDDLE, DONGLIANG ZHUANG, DENNIS D. KIM, MARK S. FINEMAN, ALAIN D. BARON

Institution: Minneapolis, MN; Portland, OR; San Diego, CA Results: This study evaluated the ability of exenatide, an incretin mimetic, to improve glycemic control in patients with type 2 diabetes and hyperglycemia on maximal doses of metformin and a sulfonylurea (SFU). Design was a triple-blind, placebo (PBO)-controlled study with a 4wk PBO lead-in and 30wk treatment period. Subjects were randomized to 5Mg subcutaneous exenatide twice daily (BID; arms A & B) or PBO for 4wks. Subsequently, arm A remained at 5Mg, arm B escalated to 10Mg. All subjects continued metformin, but to explore the risk of hypoglycemia, subjects were randomized to either maximally-effective (MaxED) or minimum-recommended (MinRD) SFU dose. The intent-to-treat population included 733 subjects (55 ± 10 y, BMI 33.6 ± 5.7 kg/m², A1C $8.5 \pm 1.0\%$; \pm SD); 82% (10Mg), 84% (5Mg), and 76% (PBO) completed. Wk30 A1C changes from baseline (\pm SE) were $-0.77 \pm 0.08\%$ (10Mg), $-0.55 \pm 0.07\%$ (5Mg), and $+0.23 \pm 0.07\%$ (PBO; adjusted $P < 0.001$ vs PBO). Mean PBO-adjusted A1C reductions were -1.0% (10Mg) and -0.8% (5Mg). A1C $\leq 7\%$ was achieved by 30% (10Mg), 24% (5Mg), and 7% (PBO) of subjects ($P < 0.001$). For MaxED arm, A1C changed by $-0.91 \pm 0.11\%$ (10Mg), $-0.67 \pm 0.10\%$ (5Mg), and $+0.16 \pm 0.10\%$ (PBO; adjusted $P < 0.001$). For MinRD arm, A1C changed by $-0.62 \pm 0.10\%$ (10Mg), $-0.43 \pm 0.10\%$ (5Mg), and $0.30 \pm 0.10\%$ (PBO; adjusted $P \leq 0.001$). At Wk30, both exenatide arms had significant weight loss from baseline (-1.6 ± 0.2 kg each exenatide arm, -0.9 ± 0.2 kg PBO; $P \leq 0.01$ vs PBO). Mild or moderate nausea was the most frequent adverse event (49% 10Mg, 39% 5Mg, 21% PBO). There was one episode of severe hypoglycemia (5Mg). The incidence of mild/moderate hypoglycemia was 28% (10Mg), 19% (5Mg), and 13% (PBO); and appeared lower with MinRD than with MaxED. In summary, exenatide was generally well tolerated and significantly lowered A1C with no weight gain in patients with type 2 diabetes unable to achieve adequate control with combined metformin-sulfonylurea therapy.

Category: Clinical Therapeutics/New Technology

DCU Comment: See earlier commentary on exenatide.

13. Effects of Exenatide (Synthetic Exendin-4) on Glycemic Control and Weight over 30 Weeks in Metformin-Treated Patients with Type 2 Diabetes

Abstract Number: 6-LB

Authors: RALPH DEFRONZO, ROBERT RATNER, JENNY HAN, DENNIS KIM, MARK FINEMAN, ALAIN BARON Institution: San Antonio, TX; Bethesda, MD; San Diego, CA

Results: This study evaluated the effects of exenatide, an incretin mimetic with potential antidiabetic activity, on glycemic control in patients with type 2 diabetes inadequately controlled with maximally

effective doses of metformin. The design was a randomized, triple-blind, placebo (PBO)-controlled, 30-wk study. After 4 wks of PBO, subjects were randomized and began 4 wks of 5 µg subcutaneous exenatide twice daily (BID; arms A and B) or PBO. Subsequently, doses in arm B were escalated to 10 Mg BID. All subjects continued metformin. There were 336 subjects in the intent-to-treat (ITT) population (age 53±10 y, BMI 34.2±5.9 kg/m², A1C 8.2±1.1%) and 272 (81%) completed the study. At Wk 30, A1C LS mean changes from baseline were -0.86±0.11% (10 Mg), -0.46±0.11% (5 Mg), and 0.00±0.11% (PBO; adjusted $P<0.01$). Of evaluable subjects, 46% (10 Mg), 32% (5 Mg), and 13% (PBO) with baseline A1C>7% (n=243) achieved A1C≤7% ($P<0.01$). Fasting and postprandial plasma glucose levels decreased in exenatide arms compared with PBO ($P<0.05$). Subjects in the exenatide arms had dose-dependent and progressive weight loss, with significant end of study reductions from baseline in both exenatide arms (10 µg: -2.8±0.5 and 5 Mg: -1.6±0.4 kg vs PBO: -0.3±0.3 kg, [$P<0.05$]). Beta-cell secretory function assessed by HOMA-B increased in both exenatide arms compared with PBO ($P<0.01$). The most frequent adverse events were generally mild or moderate and gastrointestinal in nature. No severe hypoglycemia was observed. The incidence of mild or moderate hypoglycemia was 5.3%, 4.5%, and 5.3% in the 10 Mg, 5 Mg, and PBO arms, respectively. In summary, over 30 wks exenatide significantly reduced A1C with no increase in the incidence of hypoglycemia in patients with type 2 diabetes failing maximally effective doses of metformin. Exenatide was generally well-tolerated, resulted in reduced body weight, and was associated with improved markers of B-cell function.

Category: Clinical Therapeutics/New Technology

DCU Comment: This abstract presents another affirmation of the potential of exenatide. This study supports much of what has previously been said or suggested about exenatide – the drug lowers HbA1c levels and leads to meaningful weight loss. This study further supports the notion that exenatide has very manageable side-effects and is unlikely to cause hypoglycemia, even in combination with metformin.

14. Twenty-Eight Day Dose-Response Study with Exenatide (Synthetic Exendin-4) in Subjects with Type 2 Diabetes Treated with Metformin or with Diet and Exercise

Abstract Information

Abstract Number: 598-P

Authors: TERRI H. POON, PATRIC NELSON, KATHLEEN LOVE, LARRY SHEN, THOMAS A. BICSAK, KRISTIN TAYLOR, DENNIS D. KIM

Institution: San Diego, CA

Results: This study evaluated the effects of a range of doses of exenatide, an incretin mimetic with potential antidiabetic activity, on glucose control, safety, and tolerability in subjects with type 2 diabetes treated with metformin (75% of subjects) or diet/exercise (25% of subjects). After a 2-week, single-blind placebo lead-in period, 156 subjects (67M, 89F; age 53±11 y; BMI 35±6 kg/m²; A1C 7.5±0.7%) were randomized to 28 days of triple-blind treatment in this placebo-controlled, Phase 2 study; 141 subjects completed the study. Exenatide (2.5, 5.0, 7.5, or 10.0 Mg) or an equal volume of placebo was injected subcutaneously, twice daily, within 15 min before meals in the morning and evening. Dose-dependent reductions in A1C ($P<0.0001$ for linear contrast) were observed (-0.04±0.07%, -0.27±0.08%, -0.37±0.07%, -0.49±0.08%, and -0.49±0.08% LS mean change from baseline ±SEM in the placebo, 2.5 Mg, 5 Mg, 7.5 Mg and 10 Mg arms, respectively). The magnitude of the change in A1C was consistent with the short study duration and relatively low baseline A1C in this study compared with prior studies. An end-of-study A1C ≤7% was achieved by 37% of evaluable subjects in the combined exenatide arms, versus 10% in the placebo arm. Based on a retrospective analysis, dose-dependent weight loss ($P<0.0001$ vs placebo) was observed on Day 28 (-0.1±0.3kg, -0.8±0.3kg, -0.7±0.3kg, -1.4±0.3kg, and -1.8±0.3kg change from baseline in the placebo, 2.5 Mg, 5 Mg, 7.5 Mg and 10 Mg arms, respectively). The most common adverse event was dose-dependent, transient, mild-to-moderate nausea. Two subjects in the 2.5 Mg arm experienced mild or moderate hypoglycemia, with no incidents of hypoglycemia reported at higher exenatide doses. We conclude that exenatide had dose-dependent effects on glycemic control in subjects with type 2 diabetes treated with metformin or diet/exercise. The retrospective analysis of body

weight showed reductions consistent with previously reported data. Category: Clinical Therapeutics/New Technology

DCU Comment: Although there are several abstracts that present information on the compelling clinical attributes of exenatide, we believe the weight of this evidence is hardly repetitive or tiresome. Rather, it simply buttresses the case in favor of this compound. We believe the ADA must agree, as they certainly accepted a number of posters on this subject.

15. Assessment of the Benefits from a "Polypill" To Reduce Cardiovascular Disease among Persons with Type 2 Diabetes Mellitus Abstract Information

Abstract Number: 1207-P

Authors: STEPHEN SORENSEN, MICHAEL ENGELGAU, THOMAS HOERGER, KATHERINE HICKS, K. M. VENKAT NARAYAN, DAVID F. WILLIAMSON, FRANK VINICOR, THEODORE THOMPSON, PING ZHANG, BARBARA BOWMAN

Institution: Atlanta, GA; Research Triangle Park, NC

Results: A recently published report of a "polypill" to prevent heart attacks and stroke among persons aged 55 and older may have important implications for reduction of cardiovascular disease (CVD) among persons with diabetes. The polypill would contain a statin, three blood pressure lowering drugs each at half standard dose, folic acid, and aspirin, and is estimated to reduce heart attack by 88% and stroke by 80%. We examined potential benefits of the polypill in a diabetic population using a Markov lifetime statistical model of diabetes. We simulated a cohort of males and females aged 55 and older with newly diagnosed type 2 diabetes. The intervention group received the polypill plus intensive glycemic control. The comparator group received intensive glycemic control plus cholesterol reduction, as necessary, and moderate hypertension control, as necessary. In the simulation the polypill intervention resulted in a reduction in lifetime incidence of cardiovascular disease from 32.3% to 7.8% and of stroke from 19.2% to 7.1%. Life years increased from 11.3 to 13.2. In a sensitivity analysis we assumed the polypill reduced heart attack and stroke by 44% and 40% respectively. These more conservative assumptions resulted in the reduction of lifetime incidence of heart attack to 28.2% and of stroke to 15.1%. Life years increased to 11.8. Our model suggests the polypill could provide substantial benefits by reducing cardiovascular morbidity and mortality among persons with diabetes. Further studies are needed to confirm these findings. Category: Health Care Delivery/Economics

DCU Comment: Heart disease is a well-known complication of T2DM. While proper glucose control helps, this study advances the notion that combining various compounds into a single pill can have a strong impact on improving cardiovascular health. Patient compliance is always a tricky challenge and combining several powerful medicines into one can only make things easier. We will continue to watch this one.

16. Greater Benefits of Rosiglitazone (RSG) Added to Submaximal Dose of Metformin (MET) Compared to Maximizing Metformin Dose in Type 2 Diabetes Mellitus (T2DM) Patients Abstract Information

Abstract Number: 608-P

Authors: JULIO ROSENSTOCK, BARRY J. GOLDSTEIN, MARGARET J. WOODDELL, LEANNE J. STROW, BRIAN R. WATERHOUSE, ALEXANDER R. COBITZ

Institution: Dallas, TX; Philadelphia, PA; King of Prussia, PA

Results: RSG is often added to maximal MET to provide durable glycemic benefit in T2DM patients requiring combination therapy. Increasing MET monotherapy may be associated with increased GI intolerability. In this 24-week, double-blind trial, the efficacy, tolerability and safety of adding RSG to submaximal MET (1g/d) was evaluated vs titrating to the maximal effective dose of MET (2g/d). T2DM patients on prior therapy (diet/exercise or oral anti-diabetic mono – or combination therapy) were treated with open-label MET (1g/d) and after a 4-7 week run-in period, were randomized to receive addition of blinded RSG 4mg (n=358) or MET 500mg (n=351). At week 8, the groups were uptitrated to a TDD of

8mg + 1g/d (RSG+MET) and 2g/d (MET). As designed, HbA_{1c} change from baseline at week 24 for RSG+MET was noninferior to maximal MET. However, RSG+MET was superior to MET in improvements in FPG, insulin, and HOMA-S. A greater proportion of patients in the RSG+MET group reached targets of HbA_{1c} < 7% (54.7% vs 45.0%) and FPG ≤ 126mg/dl (47.5% vs 28.8%). RSG+MET was generally safe, well tolerated and associated with fewer GI side effects than MET (28.5% vs 39.1%). Withdrawals due to GI events were lower with RSG+MET (3.1%) than MET (6.8%). Addition of RSG to submaximal MET provided significantly greater improvements in insulin resistance and response to glycemic targets compared to maximal up-titration with MET and was associated with better GI tolerability.

Category: Clinical Therapeutics/New Technology

DCU Comment: This abstract provides a strong statement supporting the notion that combining multiple classes of diabetes drugs is often more effective than simply upping the dosage of a single drug class. As TZD's are not only strong drugs in their own right, but also aid insulin re-sensitization, it is not surprising that combining TZD's with other drugs improves the overall outcome. Hopefully additional studies like this one will further convince clinicians that tinkering with the dosage of a single drug is usually not nearly as powerful as adding a new class of drugs to the mix.

17. Triple Therapy in Type 2 Diabetes (T2DM): Benefits of Insulin Glargine (GLAR) over Rosiglitazone (RSG) Added to Combination Therapy of Sulfonylurea Plus Metformin (SU+MET) in Insulin-Naive Patients Abstract Information

Abstract Number: 609-P

Authors: JULIO ROSENSTOCK, DANNY SUGIMOTO, POUL STRANGE, JOHN STEWART, ERIKA SOLTES-RAK, GEORGE DAILEY

Institution: Dallas, TX

Results: Combination SU+MET remains the most common regimen for managing T2DM; yet sustained glycemic control often calls for triple therapy. To assess the relative merits of adding basal insulin or TZD as the 3rd agent, we compared the efficacy and safety of add-on GLAR vs RSG in T2DM insulin-naïve pts on SU+MET. In this 24-wk multicenter, randomized, open-label, parallel trial, 217 pts (A1c 7.5-11%, BMI >25kg/m²) on ≥50% SU+MET received add-on GLAR 10 IU/d or RSG 4mg/d. GLAR forced-titration to target FPG ≤100mg/dL was less aggressive than in the Treat-To-Target study. RSG was increased to 8mg/d any time post-6 wks if FPG>100mg/dL. Mean age, diabetes duration, BMI, and baseline A1c (8.8-8.7%) were similar in both groups. There was a significantly higher dropout rate in the RSG group vs. GLAR (19% vs 8% p=0.005). GLAR yielded better FPG compared with RSG (-65±4mg/dL vs -46±4mg/dL; p=0.001). Change in A1c from baseline was similar (-1.7±0.1 GLAR vs -1.5±0.1 RSG). Final GLAR dose/d was 38±26 IU and 7.1±2mg for RSG. Overall hypoglycemia was similar except for more confirmed symptomatic nocturnal hypoglycemia with GLAR at <70mg/dL but not at <50mg/dL and numerically more severe events with RSG. GLAR significantly improved total cholesterol, LDL, and TG (from 196-186mg/dL, 117-115mg/dL, 217-176mg/dL, [-4%, -2%, -19%] respectively), whereas RSG raised them (196-215mg/dL, 106-120mg/dL, 214-252mg/dL [+10%, +13%, +5%] respectively) with significant treatment differences (p<0.002). RSG had significantly more weight gain than GLAR (3.0±0.4kg vs 1.6±0.4kg; p=0.02), more adverse reactions (28% vs 6%; p=0.0001) including peripheral edema (12.5% vs 0). GLAR saved \$397/patient over 24 wks. In conclusion, low-dose GLAR resulted in better FPG, and basically similar hypoglycemia profiles. Unlike RSG, GLAR was associated with fewer adverse reactions, no edema, less weight gain, and salutary lipid changes at lower cost. Conceivably, higher GLAR doses could yield even greater glycemic benefits.

Category: Clinical Therapeutics/New Technology

DCU Comment: Combination therapy is a powerful weapon in fighting T2DM, but the question remains as to the best combination; this obviously will continue to vary from patient to patient, but for years, there has been both patient and physician resistance to going on insulin sooner. This article provides an intriguing insight into this question. Instead of adding a TZD to the mix, the authors of this paper added

insulin glargine. The results were quite interesting – Lantus produced fewer adverse events, less weight gain, and importantly, was less costly than TZD's. Although the change in HbA1c levels was roughly equivalent, it's hard to argue that insulin glargine isn't a very compelling option when looking to enhance a multi-drug approach to the disease.

18. Comparison of a Multiple Daily Injection Regimen with Once-Daily Insulin Glargine Basal Insulin and Mealtime Lispro, to Continuous Subcutaneous Insulin Infusion: A Randomised, Open, Parallel Study

Abstract Information Abstract Number: 455-P

Authors: GEREMIA B. BOLLI, FABIO CAPANI, PHILIP D. HOME, DAVID KERR, REENA THOMAS, ELISABETTA TORLONE, JEAN L. SELAM, AGNES SOLA-GAZAGNES, ESTER VITACOLONNA

Institution: Perugia, Italy; Chieti, Italy; Newcastle upon Tyne, United Kingdom; Bournemouth, United Kingdom; Paris, France

Results:

Meta-analysis suggests continuous subcutaneous insulin infusion (CSII) is superior to multiple daily insulin injections (MDI) using NPH as basal insulin. The aim of this multicenter study was to establish whether MDI using the long-acting analog insulin glargine once-daily (with meal-time lispro) achieves glycemic control (HbA_{1c}) equivalent to CSII (lispro). People with Type 1 diabetes (HbA_{1c} ≤ 9.0 %) naïve to CSII and glargine were randomized and treated for 6 months with CSII (N=28) or MDI (N=29). HbA_{1c} decreased from 7.7 ± 0.7 (SD) to 7.0 ± 0.8 % with CSII, and from 7.8 ± 0.6 to 7.2 ± 0.7 % with MDI, the baseline/center adjusted difference being -0.1 (95% CI -0.5, 0.3) % (CSII vs. MDI, NS). Mean daily blood glucose (BG) level decreased from 164 ± 41 to 146 ± 32 mg/dl and from 160 ± 30 to 144 ± 20 mg/dl respectively (difference 1 (-14, 15) mg/dl (NS)). The MAGE decreased from 144 ± 43 to 115 ± 40 mg/dl (CSII) and from 137 ± 31 to 115 ± 38 mg/dl (MDI) (CSII vs MDI, NS). Coefficient of variation of eight-point BG profiles decreased from 53 ± 10 to 46 ± 8 % and from 52 ± 12 to 47 ± 11 % (NS). Confirmed hypoglycaemic events per patient (BG < 72 mg/dl) over the 6 months were not statistically different (41 ± 8 (SE) vs 35 ± 7 events, CSII vs MDI, NS). Severe hypoglycaemia was too infrequent to allow meaningful comparison (2 events in all). Average cost per treatment was 4 times more expensive with CSII.

Conclusions: both CSII and a once-daily glargine-based MDI regimen improve BG to a similar extent with no differences in mean BG, HbA_{1c}, BG excursions, and frequency of hypoglycaemia. A glargine-based MDI regimen is less expensive and therefore more cost-effective when used in an unselected population of people with Type 1 diabetes.

Category: Clinical Therapeutics/New Technology

DCU Comment: This paper presents the case that once-daily glargine and multiple daily injections can achieve the same level of glucose control but at a lower cost to pumps. While we can't ignore the notion that multiple daily injections and glargine basal insulin can work effectively for some, very few patients have a uniform basal rate throughout a 24-hour period, and it is this group that will see the best results with Lantus. Broadly, we still believe that issues of convenience, comfort, and patient compliance leave pump insulin therapy as an extremely viable treatment option. We believe although A1Cs were not much different in this study, nor was MAGE, in practice outside a study like this, we believe standard deviations would be lower with pump therapy and we'd love to see this examined in a larger, longer study.

19. Patients with Type 2 Diabetes Can Achieve A1C Targets with Once-Daily Biphasic Insulin Aspart 70/30 before Supper Abstract Information

Abstract Number: 547-P

Authors: RAJEEV JAIN, TIMOTHY WAHL, JACK WAHLEN, PETER BRESSLER, PETER HU, ELSIE ALLEN Institution: Milwaukee, WI; Omaha, NE; Ogden, UT; Dallas, TX; Princeton, NJ
Results: Currently recommended A1C targets are $\leq 6.5\%$ (ACE) and $< 7.0\%$ (ADA). The primary objective of this study was to demonstrate that biphasic insulin aspart 70/30 (BIAsp30), which provides both basal and bolus insulin coverage, can reduce A1C levels to the ACE target of $\leq 6.5\%$ when added to oral antidiabetic drug (OAD) therapy in type 2 diabetes. In this 48-week observational, multi-center, open-label trial, patients with type 2 diabetes, not achieving glycemic targets on OADs (with or without once-daily basal insulin therapy with NPH or glargine) were titrated to target blood glucose levels (80-110 mg/dl) by algorithm-directed forced titration with BIAsp 70/30. During Phase 1 of this study, patients initiated treatment with 6 U BIAsp 70/30 before supper and titrated the dose based on the average fasting plasma glucose values from 3 previous days according to the schedule below.[table1] Patients attaining an A1C value $\leq 6.5\%$ at the end of Phase 1 (at 16 weeks) were considered to have completed the study, otherwise they began twice-daily dosing (Phase 2). Forty-one of the 100 enrolled patients have been followed through Phase 1 (mean age, 58.0 ± 11.8 ; BMI, 33.6 ± 6.7 kg/m²). Two patients have discontinued. Of the 39 patients completing Phase 1, nine reached the ACE A1C target of $\leq 6.5\%$. A total of 16 subjects achieved the ADA A1C target of $< 7.0\%$. For the 9 patients achieving A1C $\leq 6.5\%$, the mean A1C was $8.2\% \pm 0.6$ at baseline and $6.2\% \pm 0.2$ at week 16; the mean daily insulin dose was $72.1 \text{ U} \pm 40.7$ (0.67 ± 0.36 U/kg); and weight increased slightly from baseline (107.3 ± 13.7 kg) to Week 16 (109.2 ± 3.4 kg). Conclusion: Currently recommended A1C targets $\leq 6.5\%$ and $< 7.0\%$ can be achieved by titrating to fasting plasma glucose levels with once-daily BIAsp 70/30, before supper.

Category: Clinical Therapeutics/New Technology

DCU Comment: A once-daily administration of insulin is certainly not an overly burdensome addition to the treatment regimen for those who have Type 2 diabetes and cannot achieve recommended HbA1c levels. This paper demonstrates that adding once-daily insulin can meaningfully improve HbA1c levels without undue weight gain. While this is an interesting presentation, we do believe it is also important to look at whether patients could do even better by adding prandial insulin as well as one-per-day; also, hypoglycemia should be examined (we will look for this data at the poster itself).

20. CJC-1131, a Long Acting GLP-1 Analog Safely Normalizes Post-Prandial Glucose Excursion and Fasting Glycemia in Type 2 Diabetes Mellitus Abstract Information

Abstract Number: 535-P

Authors: POL-HENRI GUIVARC'H, JEAN-PAUL CASTAIGNE, C. GAGNON, L. PESLHERBE, J. H. DREYFUS, DANIEL J. DRUCKER

Institution: Montreal, QC, Canada; Toronto, ON, Canada

Results: CJC-1131 is a synthetic GLP-1 analog being developed for the treatment of Type 2 diabetes (T2DM) and uses the Drug Affinity Complex (DAC) technology. After injection, covalent binding to albumin results in a long t_{1/2} of ≈ 10 days. After a 1 week washout, 25 (T2DM) patients, 20M/5F, age 60 ± 6 years (mean \pm SD), BW 94 ± 13 kg, BMI 30 ± 8 kg/m², fasting plasma glycemia (FPG) 9.5 ± 2.2 mmol/L, average 7-point glycemia (7PG) 10.8 ± 2.6 mmol/L were enrolled in a randomized, double-blind, placebo-controlled study. Twenty-two patients were treated with CJC-1131 for 14 days with a daily injection of 2, 4 or 8 Mg/kg or for 20 days with 12 Mg/kg. In the last 3 groups, patients were titrated up with 3 days at each lower dose level. Glycemic control was assessed by 7PG (mean of pre- and 2-hour post breakfast, lunch and dinner and bedtime) and standardized meal tests (SMT) performed before treatment and 48 hours after the last dose.

CJC-1131 was generally well tolerated with no signs of immunogenicity. As expected with GLP-1 agents, mild nausea and vomiting occurred in some cases. Glycemic levels were reduced in a dose-dependant manner with a significant mean 7PG reduction of up to 35% ($p=0.003$) and reduced mean FPG by up to

31% ($p=0.007$) at the dose of 12 Mg/kg. The AUC of the glucose curve above 5 mmol/L over 4-hour was reduced by more than 30% when comparing SMT 48 hours after the last dose to prior treatment. With 12 Mg/kg, pre-meals and 2-hour post meal glycemia were lowered below 7 and 11.1 mmol/L in 62.5% and 50% of patients respectively. Body weight was reduced by 1.7 to 3.0 kg in a dose-dependent manner. No cases of hypoglycemia were reported. CJC-1131 dosed once-a-day in this 14-20 day study demonstrated a dose/duration-dependent effect on glycemia and body weight. There was no sign of local irritation and the drug was well tolerated. A 12-week study is ongoing to assess the clinical profile of CJC-1131 over a longer treatment period.

Category: Clinical Therapeutics/New Technology

DCU Comment: As has been noted, GLP-1 compounds are a promising new class of diabetes drugs. Earlier this summer, CJC-1131 data was shown to much fanfare by the company, which we thought was odd for four week data, but it did look good (to the extent that conclusions can be drawn after that time period). That data was not placebo controlled and the wash out had some confusion for us, so we have been watching for follow up data, expected “mid-year.” This study is a different one; it indicates that CJC-1131 appears to lower glucose levels and lead to weight loss, without problematic side-effects to date; we look forward to seeing longer-term data.

21. The DPP-IV Inhibitor MK-0431 Enhances Active GLP-1 and Reduces Glucose Following an OGTT in Type 2 Diabetics Abstract Information

Presented during: Incretin Mimetics - 06/08/2004 (10:15 - 12:15 PM)

Abstract Number: 353-OR

Authors: GARY A. HERMAN, PENG-LIANG ZHAO, BRUNO DIETRICH, GEORG GOLOR, ANDREAS SCHRODTER, BART KEYMEULEN, KENNETH C. LASSETER, MARK S. KIPNES, DEBORAH HILLIARD, MICHAEL TANEN, INGE DE LEPELEIRE, CAROLINE CILISSEN, CATHY STEVENS, WESLEY TANAKA, KEITH M. GOTTESDIENER, JOHN A. WAGNER
Institution: Rahway, NJ; Berlin, Germany; Neuss, Germany; Brussels, Belgium; Miami, FL; San Antonio, TX

Results: MK-0431 is an orally active, potent, and highly selective dipeptidyl-peptidase IV (DP-IV) inhibitor being developed for the treatment of type 2 diabetes (T2D). DP-IV inhibitors are a new potential therapeutic approach to T2D that enhance levels of the active form of incretins, facilitating glucose-dependent insulin secretion. A randomized, placebo-controlled, 3-period, crossover study was conducted in 56 patients with T2D on diet exercise treatment to assess the glucose lowering activity as well as the safety and tolerability of single oral doses of MK-0431. Patients received single oral doses of 25-mg or 200-mg MK-0431 or placebo, separated by 7-day washout intervals. Following an overnight fast, patients had an oral glucose tolerance test (OGTT) at 2 hours post dose. MK-0431 was generally well tolerated. MK-0431 was associated with a significant reduction of glycemic excursion following the OGTT: incremental glucose AUC was reduced by approximately 22% ($p<0.001$) and 26% ($p<0.001$), for the 25- and 200-mg doses respectively, as compared to placebo. Both doses were associated with approximately 2-fold increases in active GLP-1 levels as well as the ratio of active to total GLP-1 levels following an OGTT ($p<0.001$), as compared to placebo. Doses of 25- and 200-mg were associated with increases in plasma insulin AUC (22% and 23% respectively, $p<0.001$), plasma c-peptide AUC (13% and 21% respectively, $p<0.001$) and reductions in plasma glucagon AUC (8%, $p=0.015$ and 14%, $p<0.001$ respectively), following the OGTT, as compared to placebo. The effects on glucose, active GLP-1, insulin, c-peptide and glucagon levels following the OGTT provide pharmacologic proof-of-concept for MK-0431 in patients with type 2 diabetes.

Category: Clinical Therapeutics/New Technology

DCU Comment: While this study appears mostly as a proof-of-concept for the MK-0431 compound, it is encouraging nevertheless. We believe DPP-IV inhibitors are an intriguing new class of drugs and we believe the data from this study suggests that MK-0431 could have compelling in vivo efficacy.

22. Early Initiation of Metformin and Life Style Modification Can Prevent/Delay the Onset of Type 2 Diabetes Mellitus in Patients with Overweight/Obese Impaired Glucose Tolerance Abstract Information

Abstract Number: 574-P

Authors: M. G. UVARAJ

Institution: Salem, Tamilnadu, India

Results: AIM:

To Evaluate the Effect of Diet, Exercise, Life Style Modification and Early Initiation of Metformin in Patients with Over Weight/Obese Impaired Glucose Tolerance (IGT) on Transformation of Type 2 Diabetes mellitus.

Methods:

252 Patients with IGT with Mean BMI of >28 were Randomised into 3 Groups,

I. 68 Control Group (CON),

II. 89 Intervention Group-A (INT-A) with Life Style Modifications, Diet and Physical Exercise;

III. 95 Intervention Group-B (INT-B) Diet, Exercise, Lifestyle Modification with Metformin. The Mean Duration of follow up was 22 Months.

The INT-A Group Received Dietary Advice, Counseling for weight loss, Instructions for Physical activity and Moderate exercise. While the INT-B Group in addition received Tablet Metformin 250mg to 750mg/day, according to their Glycaemic Status. At base line the Subjects had a Mean age of 38.1 +/- 4.8 years. 32 Patients were Excluded (CON-8, INT-A-11, INT-B-13), As they Failed for Follow up, OGTT Done after 19-21 months duration. The Cumulative Incidence of Diabetes ; IGT; and Normal tolerance was Calculated for each Group. Anti Hypertensive Drugs, Statins, and Fibrates were Prescribed to all the 3 Groups as and when required..

Results:

The Incidence of Diabetes in CONT Group was 33.4%; INT-A 14.8%, INT-B 5.2%. The Improvement of IGT to Normal was 5.8% in CONT Group, 45% in INT-A and, 70.9% in INT-B Group. Significant Weight Gain and Raised BMI was Observed in CON Group (29.1 +/- 3.6 at base line to 32.3 +/- 3.7 Kg/m²) The INT-A Group Observed Weight loss and BMI Decreased from (29.7 +/- 3.3 at baseline to 26.8 +/- 3.1 kg/m²) While in the INT-B Group achieved desirable Weight loss and BMI (29.9 +/- 3.6 at baseline to 24.1 +/- 3.1 Kg/m²).

Conclusion:

The Transformation of IGT to T2DM Can be Prevented/Delayed by Diet Control, Weight Reduction, Life Style Modifications and Early Initiation of Metformin

Category: Clinical Therapeutics/New Technology

DCU Comment: This abstract presents a very strong message for clinicians – the sooner that a patient changes his/her behavior, the better. T2DM is not inevitable and, if stopped early, is not permanent. This study should further drive home the point that lifestyle modification and the introduction of metformin can combine to dramatically improve outcomes if they are introduced early in care. To boot, metformin is so inexpensive!

23. Positive Effects of Metformin in Childhood Insulin Resistance Syndrome Abstract Information

Abstract Number: 678-P

Authors: SVETLANA TEN, SUNIL SINHA, AMRIT BHANGOO, NEESHA RAMCHANDANI, MARIA VOGIATZI, MARIA NEW, NOEL MACLAREN

Institution: Brooklyn, NY; New York, NY

Results: BACKGROUND:

Insulin resistance syndrome (IRS) in adolescents is a precursor of adult glucose intolerance, diabetes and PCOS.

OBJECTIVE: To evaluate the effect of metformin, coupled with carbohydrate restriction and enhanced exercise on the prevention of progression of IRS.

DESIGN/METHODS:

We treated 21 insulin resistant patients (5 males and 16 females), comprising 19 adolescents (17 ± 3 yrs) and 2 adults, with metformin 850 mg TID for 8-12 months. OGTT, lipid profile, FFA, thyroid function tests and androgen level were determined before and 12 months after treatment.

RESULTS:

All patients were overweight (BMI > 95th %), 13 (61.9%) had impaired glucose tolerance (IGT). Fifteen of 16 females had evidence of PCOS. Liver enzymes were elevated in 3 (14.2 %) cases, fasting triglycerides (TGs) were elevated in 8 (38%) cases and elevated blood pressure was seen in 4 (19%) cases.

There was no significant changes in leptin, TFT, prolactin, blood pressure, DHEA, 17-OHP, IGF-1, IGFBP-1, IGFBP-3, urinary free cortisol, Lpa, cholesterol, LDL and HDL after treatment.

However, IGT normalized in 11 cases (84.6 %), while 2 males continued to have IGT after 12 months of treatment. Importantly, insulin sensitivity calculated by the Cederholm and Matsuda indices, AUC insulin and AUC for glucose improved significantly. BMI, TGs and FFA were also significantly decreased, as did testosterone and androstendione levels in PCOS females. Improved levels of SHBG, ALT and PAI-1 activity did not reach statistical significance.

CONCLUSIONS:

Improving insulin sensitivity with metformin resulted in normalization of glucose tolerance in 84.6 % of cases and significant improvement in dyslipidemia was seen. Early intervention in cases of childhood onset of IRS can prevent its progression for at least 1 year. Tolerance to metformin was achieved by a graduated increase in dosage over 3 or more weeks.

Category: Clinical Therapeutics/New Technology

DCU Comment: While this study enrolled a very small number of subjects, the conclusions are quite interesting. Instead of holding off on drug therapy and relying on diet/exercise, this study would suggest that early intervention with drugs like metformin can be highly effective. When you consider that poor diet and exercise habits are often a major cause of T2DM, it seems very rational that adding pharmaceutical agents to the mix will lead to better outcomes.

24. Dissipating Excess Energy Stored in the Liver Is a Potential Treatment Strategy for Diabetes Associated with Obesity Abstract Information

Abstract Number: 1446-P

Authors: YASUSHI ISHIGAKI, HIDEKI KATAGIRI, TETSUYA YAMADA, YOSHITOMO OKA

Institution: Sendai, Miyagi, Japan

Results: Excess energy intake is a major cause of the explosive increase in diabetes. Increasing energy expenditure by reducing metabolic efficiency is a potential treatment strategy for type 2 diabetes associated with obesity. Uncoupling protein-1 (UCP1) generates heat instead of ATP. Ectopic expression of UCP1 may therefore increase energy expenditure and improve diabetes associated with obesity. The liver can store and release abundant fat, dynamically, in response to the energy balance, making it a potential site for ectopic expression of UCP1. In this study, using adenoviral vectors, we expressed UCP1 protein in the liver in C57BL/6 mice, after high fat chow had induced the development of diabetes with obesity.

Energy expenditure was significantly increased, by 12%, and body weight was decreased, by 13%, in UCP1-mice as compared with LacZ- (control) mice. Fat accumulation was reduced in the liver as well as in brown and epididymal adipose tissues in UCP1-mice. Markedly reduced SREBP-1c expression and enhanced AMPK phosphorylation in the liver appear to be the mechanisms underlying improvement of fatty liver findings. In addition, blood glucose levels and lipid parameters were decreased and insulin tolerance test revealed marked improvement of insulin sensitivity in UCP1-mice. Plasma leptin levels were decreased (by 56%) despite decreased food intake in UCP1-mice, suggesting improvement of

hypothalamic leptin sensitivity. These results suggest that hepatic UCP1 expression exerts not only local effects in the liver but also remote effects in adipose and the hypothalamus, thereby, improving the obesity, diabetes and dyslipidemia induced by high fat chow. In contrast, intriguingly, under standard chow conditions, hepatic UCP1 expression exerted minimal effects on energy expenditure, body weight, adiposity and blood glucose levels, suggesting that hepatic UCP1 expression dissipates only surplus energy without affecting required energy. Thus, uncoupling in the liver is a new potential therapeutic target for the metabolic syndrome.

Category: Integrated Physiology

DCU Comment: This is a very interesting new approach to the problem of obesity. While such a direct interference in the normal operation of the liver may be problematic in humans, its an interesting new approach to the problem. We would not be surprised to see further research along these lines.

25. Heterozygous Crebbp Deficiency Almost Completely Prevents Obesity and Diabetes in Ob/Ob Mice

Abstract Number: 1712-P

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Results: Leptin and adiponectin may be two of major insulin sensitizing hormones secreted from adipose tissue. Crebbp (cAMP response element binding protein (CREB) binding protein) heterozygous deficient (Crebbp ? +/-) mice with increased leptin sensitivity and increased plasma adiponectin levels exhibited markedly reduced body fat and increased insulin sensitivity. In this study, to clarify the relative contributions of leptin in the prevention against obesity and insulin resistance by heterozygous Crebbp deficiency, we studied Crebbp ? +/- mice crossed with leptin deficient Lepob/ob mice. Interestingly, Crebbp ? +/- Lep ob/ob mice were completely protected from obesity and largely protected from diabetes induced by leptin deficiency. Moreover, adiponectin transgenic Lep ob/ob mice with elevated plasma concentrations of adiponectin, which were similar to those of Crebbp ? +/- Lep ob/ob mice, showed partial amelioration of diabetes, but showed almost the same body weight as Lep ob/ob mice. These data suggested that CBP appeared to regulate body weight and insulin sensitivity via both adiponectin/leptin-independent and -dependent pathways. To look for the molecules regulating insulin sensitivity and/or body weight independently of leptin, we searched for molecules whose expression were changed in Crebbp ? +/- Lep ob/ob mice, and found that expression of various kinds of molecules including secreted proteins such as adipisin, membrane proteins such as AdipoR1/2, and transcription factors such as HNF3 were changed. These transcription profiling should facilitate the identification of novel potential targets for obesity and diabetes therapeutics independent of leptin.

Category: Obesity

DCU Comment: A very interesting study. While it is far too early to get overly excited about findings like these, it is an intriguing new direction for scientists to explore in greater detail.