

Missing the Point: Substituting Exenatide for Nonoptimized Insulin

Going from bad to worse!

The recent American Diabetes Association/European Association for the Study of Diabetes consensus treatment algorithm for type 2 diabetes has advanced basal insulin treatment as a much earlier therapeutic option following a structured target-driven strategy (1). However, the misconception by both providers and patients that insulin should be regarded as the therapy of last resort still prevails and is perhaps the main barrier to insulin treatment, even at the price of many years of poor glycemic control. Insulin is the most effective diabetes agent, only limited by hypoglycemia; however, when used inappropriately in nonphysiological and nonoptimized regimens, many patients treated with insulin remain poorly controlled (2).

In the last decade, several new treatments have been developed for treating type 2 diabetes. It is conceivable that the initial American Diabetes Association/European Association for the Study of Diabetes consensus algorithm may eventually be revised to include additional therapeutic options for early use in combination with metformin once evidence regarding sustained efficacy and safety accumulates (3). New agents have been tested in combination with insulin with the main purpose of establishing a “proof of concept” of an independent effect by keeping insulin therapy unchanged or not optimized. However, this “regulatory approval approach” often resulted in relatively small A1C reductions, and at the end of the trials the mean levels often remained far above the desired A1C targets (4–6). Although some of these combinations may provide benefits such as reduced insulin resistance, less weight gain, lower insulin requirements, and possibly less hypoglycemia (4–7), none of these secondary gains can substitute for the primary objective of reaching the recommended glycemic targets.

The concept of adding a new therapy to insulin was the initial strategy employed with troglitazone to get fast regulatory approval in 1997. The concept of using an insulin sensitizer along with insulin to im-

prove glycemic control and reduce insulin requirements was quickly embraced following the study of add-on troglitazone (4). The makers of troglitazone then unleashed an aggressive marketing campaign, including direct-to-consumer advertising (some may still remember the full-page newspaper ads), reinforcing the misconception against insulin and possibly further delaying initiation of insulin therapy in many patients. Although subsequent trials with glitazones in combination with insulin showed only modest improvements in glycemic control, this strategy also led to misguided attempts to substitute newer agents for insulin treatment with the false concept of “rescuing” patients from insulin therapy. Since then, attempts have been made with other drugs to replace insulin therapy.

In this issue of *Diabetes Care*, Davis et al. (8) report on a small study exploring the safety of substituting exenatide for insulin therapy in an attempt to take patients off insulin. The scientific value is rather unclear, but the marketing appeal is quite obvious. In this study, success in the exenatide group was predefined as the ability to “maintain” glycemic control, allowing for a worsening of A1C no greater than 0.5%, despite the fact that the glucose control was poor to begin with. Presumably, the concept of coming off insulin, as if this was the main purpose in and of itself, appeared very appealing to patients and marketing strategists. However, we wonder whether the patients were really “successful” in stopping insulin and switching to exenatide if baseline A1C went up from 8.1 to 8.4%. Let us not forget that our main mission when managing patients with diabetes is to improve glycemic control and that the definition of real clinical success should be the achievement of A1C <7% or as close to normal as possible without unwanted side effects.

Incretin-related therapies are an important addition to our current treatment armamentarium for type 2 diabetes (9). However, what has made the marketing of exenatide most attractive to clinicians and patients is the associated weight reduction, which is rather modest in the controlled

clinical trials (10–13) but seems to be overemphasized in the periodically reported, uncontrolled, long-term follow-up of a smaller population of responders (14). This has possibly led to its off-label use for weight loss purposes rather than being used primarily for improving glycemic control.

This pilot study clearly demonstrates negative results at best. Although withdrawal of insulin therapy led to some weight loss, which was further compounded by the weight-reducing effects of exenatide, the overall effect on glycemic control was rather disappointing. The level of glycemic control was no different in patients who continued on insulin, but it is important to recognize that the insulin regimen used in this study was often nonphysiological and that no attempt was made to optimize insulin therapy. This is a serious design flaw in the study that could be construed to have been intentionally set up to demonstrate superiority of exenatide, which was used at its maximum dose, whereas there was considerable room for adjusting up the insulin therapy.

Most importantly, the glycemic control at the end of the study was poor with exenatide therapy. In the intention-to-treat group, A1C increased by 0.3% from a baseline of 8% and almost 40% of patients (nonresponders to exenatide) experienced a significant deterioration in glycemic control as shown by a 1.6% rise in A1C. Obviously, if one looks just at the “successful” 60% group of responders, the A1C decreased by 0.5% from a baseline of 8.1%, and weight was reduced by ~4 kg. However, 4 of 18 of these “successful” patients dropped out of the study between weeks 8 and 16, which does not bode well for the long-term success of such therapy. Were these patients really successful by the gold standards of clinical care? Was it worth it? Of course not! This was clearly a negative trial, with a flawed study design and a conclusion that perhaps should have been stronger against substituting exenatide for insulin. Of concern, the results of this study have the potential to be misinterpreted, and we

hope that we will not see educational messages or marketing headlines that may mislead patients and providers, such as "Exenatide successfully replaced insulin in type 2 diabetes resulting in improved glucose control and weight loss!" or "More than 50% of type 2 diabetic patients on insulin therapy can be successfully switched to exenatide!"

Negative studies are rarely published because of author and reviewer biases. Nevertheless, we feel that the journal was correct in accepting this study for publication so that the readers can learn what *not* to do with exenatide and insulin therapy. Furthermore, this study raises issues about commercial bias in study design, interpretation, and reporting by the pharmaceutical sponsors, an issue being addressed by recent guidelines from the Association of American Medical Colleges (<http://www.aamc.org/research/clinicaltrials/reporting/start.htm>). Rather than building strategies to replace insulin, we urge the study sponsors to devote efforts in well-designed studies to explore the use of exenatide with insulin to achieve true treatment success with excellent glycemic control, some weight loss, and less hypoglycemia.

Indeed, the publication of this study should stimulate the discussion in a different direction such that efforts be directed to explore the potential role of glucagon-like peptide (GLP)-1 receptor agonists in combination with insulin. A possible new concept may develop with studies properly designed to demonstrate that it is possible, even at the late stage of the natural history of the disease, to improve islet cell function with GLP-1 analogs and to facilitate reaching glycemic targets with insulin therapy. Anecdotal, such a combination is being used in practice, although there are no randomized controlled trials demonstrating the efficacy and safety of such a combination, and it is not approved by the Food and Drug Administration. Clearly, the combination of a long-acting basal insulin analog (to control the postabsorptive period) with a GLP-1 receptor agonist (to control postprandial glucose) is an obvious approach that theoretically could restore physiology through pharmacology.

We therefore encourage investigators to explore innovative approaches to improve glycemic control in patients treated with insulin using combinations of drugs that impact the endocrine system along with insulin, rather than as a substitute for insulin. Such combinations might help alleviate some of the problems of insulin

therapy, such as weight gain and hypoglycemia. Any such studies must use insulin therapy with treatment algorithms designed to get patients to optimal glycemic control, following the "Treat-to-Target" paradigm (15) rather than usual care. The aim of the trials should be to define the best treatment strategy for patients rather than to attempt to show that newer therapies can replace insulin—in our opinion, an exercise in futility. Until such studies are done, we encourage practitioners to follow guidelines and recommendations based on randomized controlled clinical trials that will help achieve glycemic goals without putting patients at unnecessary risk. Clearly, as of today, substitution of insulin with newer therapies is inappropriate.

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References

1. Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, Zinman B: Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 29:1963–1972, 2006
2. Rosenstock J, Banarer S, Owens D: Insulin strategies in type 1 and type 2 diabetes mellitus. In *Clinical Diabetes*. Fonseca V, Ed. Philadelphia, Saunders, 2006, p. 371–394
3. Rosenstock J, Zinman B: Dipeptidyl peptidase-4 inhibitors and the management of type 2 diabetes mellitus. *Curr Opin Endocrinol Diabetes Obes* 14:98–107, 2007
4. Schwartz S, Raskin P, Fonseca V, Graveline JF, the Troglitazone and Exogenous Insulin Study Group: Effect of troglitazone in insulin-treated patients with type II diabetes mellitus. *N Engl J Med* 338:861–866, 1998
5. Raskin P, Rendell M, Riddle MC, Dole JF,

Freed MI, Rosenstock J, the Rosiglitazone Clinical Trials Study Group: A randomized trial of rosiglitazone therapy in patients with inadequately controlled insulin-treated type 2 diabetes. *Diabetes Care* 24:1226–1232, 2001

6. Rosenstock J, Einhorn D, Hershon K, Glazer NB, Yu S: Efficacy and safety of pioglitazone in type 2 diabetes: a randomized, placebo-controlled study in patients receiving stable insulin therapy. *Int J Clin Pract* 56:251–257, 2002
7. Fonseca V, Schweizer A, Albrecht D, Baron MA, Chang I, Dejager S: Addition of vildagliptin to insulin improves glycaemic control in type 2 diabetes. *Diabetologia* 50:1148–1155, 2007
8. Davis SN, Johns D, Maggs D, Xu H, Northrup JH, Brodows RG: Exploring the substitution of exenatide for insulin in patients with type 2 diabetes treated with insulin in combination with oral antidiabetes agents. *Diabetes Care* 30:2767–2772, 2007
9. Drucker DJ, Nauck MA: The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 368:1696–1705, 2006
10. Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD: Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care* 27:2628–2635, 2004
11. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD: Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 28:1092–1100, 2005
12. Kendall DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS, Baron AD: Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care* 28:1083–1091, 2005
13. Zinman B, Hoogwerf BJ, Durán García S, Milton DR, Giaconia JM, Kim DD, Trautmann ME, Brodows RG: The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med* 146:477–485, 2007
14. Buse JB, Klonoff DC, Nielsen LL, Guan X, Bowlus CL, Holcombe JH, Maggs DG, Wintle ME: Metabolic effects of two years of exenatide treatment on diabetes, obesity, and hepatic biomarkers in patients with type 2 diabetes: an interim analysis of data from the open-label, uncontrolled extension of three double-blind, placebo-controlled trials. *Clin Ther* 29:139–153, 2007
15. Rosenstock J, Riddle M: Insulin therapy in type 2 diabetes. In *The CADRE Handbook of Diabetes Management*. New York, Medical Information Press, 2004