



## Potential Advantages of a Basal–Bolus Regimen Using Insulin Glulisine as Prandial Insulin

a report by

**Francisco Javier Ampudia-Blasco**

Associate Professor of Medicine, Department of Endocrinology, Nutrition and Metabolism, Clinic University Hospital of Valencia

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Several interventional studies have demonstrated that achieving near-normal glycaemic control by means of intensive insulin therapy is the best strategy to avoid and slow the progression of chronic complications in type 1 and type 2 diabetes.<sup>1–3</sup> Interestingly, the benefits of intensive treatment seem to extend over time, at least in people with type 1 diabetes, as shown in the Epidemiology of Diabetes and Interventions and Complications (EDIC) trial.<sup>4</sup> However, intensive insulin therapy using multiple daily injections (MDIs) or continuous subcutaneous insulin infusion (CSII) increased the risk of severe hypoglycaemia about three-fold.<sup>1</sup> One of the probable explanations behind this observation was the use of unphysiological insulin formulations, because both regular human insulin (RHI) and isophane insulin (NPH) are far from ideal as insulin replacements.

In the last 15 years, new insulin formulations have been coming into the market. First, short-acting insulin analogues (SAIAs) were developed to reproduce the physiological prandial insulin response, which is rapid, powerful and of short duration.<sup>5</sup> More recently, long-acting insulin analogues (LAIAs) were introduced to replace basal insulin secretion, which is peakless, sustained and necessary to avoid excessive hepatic glucose production.<sup>5</sup> Insulin glulisine is the most recently marketed SAIA – beside insulin lispro and insulin aspart – and is available to be used as prandial insulin in adults with type 1 and type 2 diabetes. In this article, the potential advantages of insulin glulisine will be discussed, as well as its role as prandial insulin in a basal–bolus regimen.

### Insulin Glulisine – A New Formulation

The SAIA glulisine (rDNA origin, Sanofi-Aventis, Inc.) is produced by recombinant DNA (rDNA) technology using a non-pathogenic strain of *Escherichia coli* (K12). Insulin glulisine is a modified human insulin in which the amino acid asparagine at position B3 is substituted with lysine, and the amino acid lysine at position B29 with glutamic acid (see *Figure 1*). These changes allow insulin glulisine to dissociate

rapidly after subcutaneous (SC) injection, which results in a fast absorption from tissue into circulation. Additionally, insulin glulisine uses polysorbate 20 as a stabilising agent instead of zinc, which is used with insulin lispro and insulin aspart. This unique formulation is associated with a reduced hexamer and dimer formation in comparison with other SAIAs, favouring a more rapid absorption.<sup>6</sup> These characteristics of insulin glulisine result in a pharmacokinetic (PK) profile that closely mimics the normal insulin response after meals.

Compared with RHI insulin, glulisine has equivalent bioefficacy but faster absorption and lower mean residence time.<sup>7</sup> In this study, insulin glulisine was also compared with insulin lispro, demonstrating similar PK and pharmacodynamic (PD) profiles.<sup>7</sup> Insulin glulisine is well absorbed irrespective of the injection site, although a slightly more rapid absorption was demonstrated when administered into the abdominal area.<sup>8</sup> The short-acting profile of insulin glulisine is also maintained across different ethnic groups, paediatric patients and subjects with altered renal function.<sup>9–11</sup>

The potential advantages of insulin glulisine in obese subjects deserve a separate commentary. It is well known that increased SC thickness alters insulin absorption, shifting the time–action profile curves to the right.<sup>12</sup> In a phase I, randomised, euglycaemic clamp study, a group of non-diabetic obese subjects received a single injection of insulin glulisine, insulin lispro or RHI (0.3U/kg SC).<sup>13</sup> As expected, time to onset of glucose infusion was shorter, and maximal glucose insulin rates were greater for insulin glulisine and insulin lispro compared with RHI (see *Figure 2*). However, insulin glulisine differed from insulin lispro and RHI in that there was no significant correlation between skin thickness and body mass index (BMI) and the time to maximal concentration. In other words, it seems that insulin glulisine maintains its rapid-acting properties more consistently in obese individuals compared with insulin lispro and RHI.

### Insulin Glulisine – Efficacy and Safety

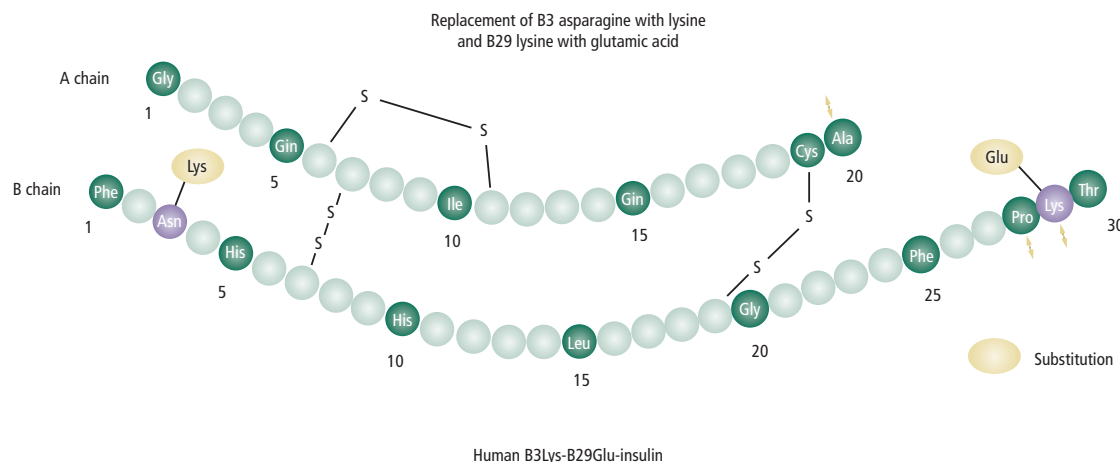
#### In Type 1 Diabetes

There are not many published studies comparing different SAIAs with RHI using the same LAIA in all arms. When insulin glargine is used in the evening as basal insulin by people with type 1 diabetes, no differences in reducing glycated haemoglobin (HbA<sub>1c</sub>) were found after 26 weeks between insulin lispro or insulin aspart, administered just before meals, and RHI injected 30 minutes before the meals, when all patients were instructed similarly in carbohydrate counting.<sup>14</sup> However, in a recent published study with a larger number of patients but of shorter duration (only 12 weeks), insulin glulisine administered just before meals demonstrated a significantly greater reduction in



Francisco Javier Ampudia-Blasco is an Associate Professor of Medicine in the Department of Endocrinology, Nutrition and Metabolism at the Clinic University Hospital of Valencia. He is also the Co-ordinator of the Diabetes Reference Unit and a Staff Endocrinologist at the same institution. Dr Ampudia-Blasco is Director of *Avances en Diabetologia*, the official journal of the Spanish Diabetes Association (SED), a member of the Editorial Committee for *Infusystems Latina* and a reviewer for *Diabetes Care* and *Diabetologia*. He received a doctorate in medicine from the Autonom University of Barcelona in 1994, completed a research fellowship in the Department of Nutrition and Metabolism – a World Health Organization (WHO) collaborating centre – at the Heinrich Heine University, Düsseldorf, and attended medical school at the University of Valencia between 1980 and 1987.

E: Francisco.J.Ampudia@uv.es

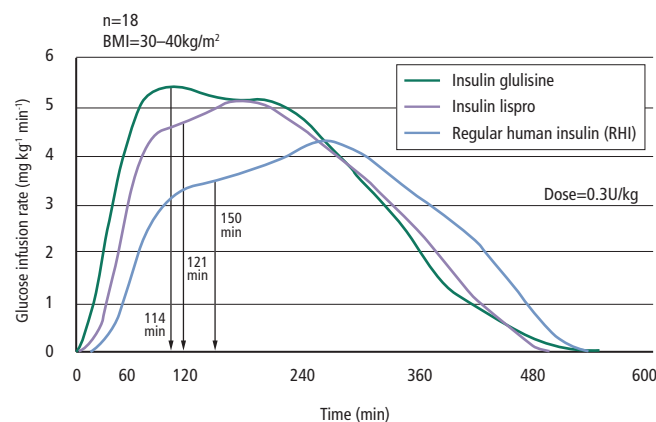
**Figure 1: Molecular Structure of Insulin Glulisine**

Insulin glulisine differs from endogenous human insulin by only two amino acid substitutions – asparagine in position B3 replaced with lysine, and lysine at position B29 replaced with glutamic acid. These two B-chain substitutions reduce dimer and hexamer formation and retain monomers, favouring a more rapid absorption compared with regular human insulin (RHI).

HbA<sub>1c</sub> compared with RHI injected 30 minutes before meals, or insulin glulisine after – or 20 minutes after starting – the meal (-0.26% versus IRH -0.13% versus glulisine after the meal -0.11%;  $p < 0.01$ ).<sup>15</sup> Although the clinical relevance of this finding is a matter of discussion, this study suggests that insulin glulisine may be injected either immediately before or at the end of a meal, increasing the flexibility of insulin administration.

In another multicentre, randomised, parallel-group study, the efficacy and safety of insulin glulisine was compared with insulin lispro in adults with type 1 diabetes, using insulin glargine once daily in the evening as basal insulin.<sup>16</sup> In this study, both SAIs, which were administered 0–15 minutes before meals, achieved similar reductions of HbA<sub>1c</sub> at 26 weeks ( $-0.14 \pm 0.04\%$ ), although higher total daily insulin doses were necessary in patients using insulin lispro. At the end of the study basal insulin dose remained unchanged with insulin glulisine but increased with insulin lispro (adjusted mean change  $+0.12$  IU in the insulin glulisine group versus  $+1.82$  IU of insulin glargine;  $p = 0.0001$ ), although prandial insulin needs were similarly reduced in both arms (adjusted mean change of  $-1.07$  IU in the insulin glulisine group and  $-0.81$  IU in the lispro group, not significant (NS)). There were no differences between the groups in symptomatic hypoglycaemia (overall, nocturnal and severe) or in weight changes. The clinical relevance of the small divergences in basal and total daily doses found in this study remains to be established.

An increasing proportion of people with type 1 diabetes use insulin pump therapy. CSII is considered as an alternative to MDI for those patients who are unable to achieve the glycaemic goals.<sup>17</sup> To assess the safety of insulin glulisine in pumps, a 12-week multinational, parallel, randomised, controlled trial using insulin aspart as comparator was designed in adults with type 1 diabetes ( $n = 59$ ) under CSII therapy.<sup>18</sup> Regarding safety issues, only seven patients (20.7%) in the insulin glulisine group reported at least one episode of unexplained hyperglycaemia ( $>350$  mg/dl) compared with 14 patients (40.0%) in the insulin aspart group, although this difference was not statistically significant. Additionally, four patients (13.8%) in the insulin glulisine group versus eight patients (26.7%) in the insulin aspart group experienced at least one catheter occlusion; however, this difference,

**Figure 2: Effect of Insulin Glulisine in Obese Non-diabetic Subjects**

Pharmacodynamic (PD) profiles following subcutaneous (SC) injection of  $0.3 \text{ U kg}^{-1}$  of insulin glulisine, insulin lispro or RHI in the abdominal area. Insulin glulisine maintains its rapid-acting properties more consistently in obese non-diabetic individuals (body mass index (BMI) range 30–40 kg/m<sup>2</sup>) compared with insulin lispro and RHI, which show a shift to the right in their time-action profiles.

again, was not statistically significant. Other evaluated variables, such as change of HbA<sub>1c</sub> from baseline, self-monitored blood glucose profiles, mean total insulin dose and frequency of hypoglycaemia, were comparable between groups. Therefore, insulin glulisine can be considered a safe alternative to other SAIs for patients with type 1 diabetes on insulin pump therapy. Although the catheter change rate and time between catheter changes were comparable between groups, an emerging question from this study is whether insulin glulisine, formulated with polysorbate 20 as stabilising agent and in solution mainly as dimers and monomers, is more stable in pumps than insulin aspart (or insulin lispro), which in solution aggregates forming hexamers with zinc to achieve sufficient stability. Further studies in this field should clarify this question.

### In Type 2 Diabetes

The efficacy and safety of insulin glulisine in comparison with RHI in patients with type 2 diabetes have been explored in a multicentre, randomised, 26-week clinical trial.<sup>19</sup> All patients – who were on insulin therapy for six months before inclusion in the study – used twice-daily

NPH insulin as basal insulin during the trial. Insulin glulisine and RHI were administered at least twice daily before breakfast and dinner, allowing immediate self-mixing with NPH when injecting with a syringe. Insulin glulisine was administered 0–15 minutes before breakfast and dinner, whereas regular insulin was administered 30–45 minutes before. Finally, 58% of the patients also used oral hypoglycaemic agents (OHAs) before and during the study. At the end of the trial, insulin glulisine achieved a significantly greater reduction of HbA<sub>1c</sub> compared with RHI (−0.46 versus 0.30%;  $p < 0.05$ ), although this difference was also evident from week 12 onwards. Furthermore, patients in the insulin glulisine group reported consistently lower blood glucose values two hours after breakfast (156mg/dl versus 162mg/dl;  $p < 0.05$ ) and two hours after dinner (154mg/dl versus 163mg/dl;  $p < 0.05$ ) compared with those in the RHI group. To my knowledge, this is the first reported study in subjects with type 2 diabetes in which an SAIA demonstrates significant HbA<sub>1c</sub> reductions with respect to RHI. However, as the authors stated in the discussion, the small difference in HbA<sub>1c</sub> between groups is of unclear significance.

## Basal–Bolus Therapy with Insulin Glulisine in Clinical Practice

### In Type 1 Diabetes

After the Diabetes Control and Complications Trial (DCCT), there is no doubt that intensive insulin therapy (also known as basal–bolus therapy) is the first-line treatment for patients with type 1 diabetes. Intensive insulin therapy implicates self-administration of insulin based on frequent home blood glucose monitoring (HBGM). To gain more flexibility, subjects with type 1 diabetes learn to calculate insulin doses according to the carbohydrate content of the meal, pre-meal glucose values and the programmed activity after the meal. Additionally, target glucose values before and after meals should be set individually because of different lifestyles.

A basal–bolus strategy can be implemented only with MDI or CSII. SAIs (lispro, aspart, glulisine) are preferred as prandial insulin by most patients (and physicians) because they can be injected just before meals or even after the meal. RHI should be injected 30–45 minutes prior to meals to prevent extended post-prandial hyperglycaemia. However, the majority of patients do not follow this recommendation,<sup>20</sup> which causes peak concentrations of insulin to occur later, putting patients at risk of late hypoglycaemia and necessitating defensive snacking to avoid hypoglycaemia.

Insulin lispro, insulin aspart and insulin glulisine have similar PK/PD properties.<sup>21–24</sup> In general, administration of SAIs results in higher insulin concentration achieved in half the time compared with RHI.<sup>25</sup> SAIs reduce the post-prandial glycaemic excursions and diminish the incidence of late hypoglycaemia more effectively than RHI.<sup>25</sup> In combination with intermediate basal insulin (NPH or ultralente insulin), SAIs were able to reduce two-hour post-prandial blood glucose levels and the frequency of hypoglycaemia (overall and nocturnal) in comparison with RHI,<sup>26–28</sup> but not to translate these advantages in reduction of HbA<sub>1c</sub>. Before the introduction of LAIs, SAIs were more effective than RHI only with CSII or with complicated basal strategies using as many as four injections of NPH insulin.<sup>29</sup> Recently, it has been demonstrated that SAIs in combination with LAIs (glargine at dinner or bedtime) are more effective in reducing HbA<sub>1c</sub> than in combination with NPH insulin four

times a day.<sup>30</sup> Additionally, a basal–bolus therapy with SAIA in combination with LAI is associated with less glycaemic variability and less risk of hypoglycaemia than with NPH insulin.<sup>31</sup>

In clinical trials insulin glulisine has demonstrated that it is as effective as insulin lispro and more effective than RHI in combination with insulin glargine in MDI therapy. Also, the safety and efficacy of insulin glulisine and insulin aspart were similar under CSII therapy. Recent observational data suggest that, in patients suboptimally controlled with other prandial insulins, initiation and optimisation of insulin glulisine in combination with insulin glargine will reduce HbA<sub>1c</sub> in the follow-up.<sup>32</sup>

To achieve maximal efficacy, insulin glulisine should be administered shortly before meals following the same principles of intensive insulin therapy. However, it has been shown that insulin glulisine may also be injected after meals, as has been demonstrated for other SAIs. This advantage may be of particular value in patient groups including older patients at risk of hypoglycaemia, children or patients hospitalised due to unpredictable eating habits.

### In Type 2 Diabetes

Insulin therapy is not usually the first-line therapeutic option in patients with type 2 diabetes. Many patients are treated initially and well maintained with diet and exercise in combination with one or two OHAs. However, as disease progresses due to steady decline in  $\beta$ -cell function, insulin therapy is required to achieve and maintain appropriate glycaemic control. Although different strategies are possible to initiate insulin therapy, the addition of basal insulin to previous OHA therapy is the simplest regimen to begin with.<sup>33,34</sup> Nevertheless, as patients get closer to target HbA<sub>1c</sub> (6.5–7.0%), post-prandial hyperglycaemia seems to contribute more to overall glycaemic control, making the addition of mealtime (prandial) insulin even more important.<sup>35</sup>

Therefore, the addition of prandial insulin to improve long-term glycaemic control is needed for an increasing proportion of patients with type 2 disease. Many patients are transferred to twice-daily (or even three-times-daily) pre-mixed insulin, in part because these formulations eliminate the need for patients to mix their own insulins. In recent years, several pre-mixed insulin formulations with SAIA (25% lispro/75% neutral protamine lispro (NPL), 50% lispro/50% NPL, aspart 30%/neutral protamine aspart (NPA) 70%), offering better post-prandial glycaemic control, have come into the market, displacing traditional pre-mixed insulin preparations with RHI,<sup>36</sup> which are becoming less readily available. However, pre-mixed insulin formulations provide only limited flexibility for specific insulin adjustments as the dose of one insulin cannot be altered without altering the other, limiting the ability to offer optimum glycaemic control.<sup>37</sup>

Therefore, new strategies, including basal–bolus therapy, are currently being tested in patients with type 2 diabetes. The addition of increasing prandial insulin injections to cover main meals will be an acceptable alternative for many patients (basal plus strategy). This approach is the logical step forwards after failure of basal insulin in combination with OHA and may facilitate the intensification of insulin therapy in selected patients.<sup>38</sup> When prandial insulin is introduced, it is recommended that secretagogues are stopped (sulphonylureas or glinides).<sup>39</sup> Recently, a basal–bolus regimen including insulin glulisine as prandial insulin three times a day and insulin glargine as basal

insulin was very effective in reducing HbA<sub>1c</sub> in obese patients with type 2 diabetes.<sup>40</sup>

It is well known that the majority of patients with type 2 diabetes are obese or overweight. In fact, obesity is a risk factor for type 2 diabetes, with 57% of cases being directly attributed to obesity.<sup>41</sup> Obesity and the thickness of the subcutaneous fat layer are also being recognised as important key factors that influence the absorption of insulin. While LAIAs have been extensively studied in type 2 patients, SAIAs are far less well characterised in these subjects, particularly those who are obese. Preliminary data suggest that insulin absorption is retarded in obese subjects with type 2 diabetes. An explorative study in obese subjects without diabetes that compared PK/PD properties of RHI, insulin lispro and insulin glulisine suggests that only insulin glulisine may maintain its short-acting properties irrespective of increased SC thickness or BMI associated with obesity.<sup>13</sup> Although further studies are necessary to confirm this observation, these data may confer some advantages to insulin glulisine as an SAIA in obese subjects with type 2 diabetes.

## Conclusions

Basal–bolus therapy is necessary in patients with type 1 diabetes and will also be required in many patients with type 2 diabetes to achieve and maintain HbA<sub>1c</sub> at treatment goals. Basal–bolus therapy consists of a combination of SAIAs and LAIAs that act as a substitute for physiological insulin secretion. Insulin glulisine, the latest SAIA coming into the market, has been synthesised by recombinant DNA technology, substituting two amino acids of the B chain of human insulin, and has been formulated without zinc. As an SAIA, insulin glulisine has a more rapid absorption and shorter duration of action than RHI, and PK/PD profiles comparable with insulin lispro. It can also be injected just prior to meals. In addition, insulin glulisine appears to have a more consistent rapid time–action profile compared with insulin lispro in obese subjects. Insulin glulisine is well tolerated and can be used safely in adult patients with type 1 or type 2 diabetes. In patients under CSII therapy, insulin glulisine has been shown to be as safe and effective as insulin aspart. In summary, insulin glulisine is a new SAIA with a unique formulation indicated to be used as prandial insulin in basal–bolus regimens in patients with type 1 and type 2 diabetes. ■

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