
Recombinant insulin in type 2 diabetes treatment: where are we now?

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Abstract: Several insulin formulations are currently available for clinical use, including human regular and protaminated insulins, rapid- and long- acting analogs and premixed combinations, which can be used in different regimens. However, there is no consensus on which are the insulin formulation and the insulin regimen of choice, especially in type 2 diabetes. Overall, insulin analogs are preferred for their better pharmacological properties with a minor hypoglycaemic risk, whereas their superiority in reducing HbA1c levels is still debated. Despite the impressive steps undertaken so far, insulin therapy is still too complex and burdensome, and even with an intensified regimen, only a modest percentage of subjects reaches HbA1c goals. New insulin formulations and devices are currently awaited to better fulfill the still unmet needs of insulin therapy.

Keywords: Insulin Analogs, Type 2 Diabetes, Hypoglycaemia, HbA1c

1. Recombinant Human Insulins

Since 1922, when substitutive therapy with insulin extracted from animal pancreas was initiated, medical research has made a great effort to reproduce the physiological insulin profile, i.e., a basal insulin secretion to control hepatic glucose output and insulin peaks to overcome postprandial glucose (PPG) excursions. In most countries, two formulations of human insulin, synthesized by recombinant DNA technique, are into the market, namely Regular Human Insulin (RHI) and the intermediate-acting Neutral Protamine Hagedorn (NPH).

RHI is a molecular hexamer, which must break down into monomers to be absorbed by subcutaneous (s.c.) tissue. Its slow onset and relatively long duration of action and the need to take injections 30–45 minutes prior to meal represent important limitations to its use [1, 2]. Furthermore, RHI peak concentrations may not occur until 2–4 hours after injection, exposing the patient to postprandial hyperglycemia and the risk of subsequent hypoglycaemia [1, 2]. NPH insulin can be used to replace or supplement basal insulin, but its profile shows a distinct peak and a limited duration of action, that does not mirror the flat physiological basal insulin secretion [1,2].

2. Rapid- Acting Insulin Analogs

Insulin analogs, i.e. modified recombinant human insulins, were developed to overcome the pharmacokinetic (PK) and pharmacodynamic (PD) limitations of RHI and NPH (Table 1) [1,2]. Insulin lispro, aspart, and glulisine are the three currently available rapid acting analogs (RAAs) [3]. Lispro, the first to get the market, has been obtained by exchanging proline at position B28 with lysine at position B29 (LysB28, ProB29) in insulin chain [4]; in insulin aspart (AspB28) proline B28 is substituted with aspartic acid [5], and glulisine has two amino acids substitutions, i.e. B3 lysine instead of asparagine and B29 glutamic acid for lysine [6]. Thanks to these structural modifications at crucial sites of the insulin molecule, all RAAs are characterized by reduced tendency for self-association, faster absorption, higher peak serum levels, and shorter duration of action, when compared with RHI.

However, despite their pharmacological superiority, comparative clinical data with RHI yielded conflicting results. A meta-analysis by Plank et al. [7], including 42 randomized controlled trials (RCTs) with over 7900 patients with type 1 (T1DM), type 2 (T2DM) or gestational diabetes, demonstrated a small but significant improvement of HbA1c only in T1DM, but no differences in T2DM patients. Con-

versely, another meta-analysis [8], analyzing data from 13 RCTs on T2DM, showed that RAAs provided a better control of HbA1c and postprandial glucose (PPG) over RHI, without any significant difference in the overall rate of severe hypoglycaemia, thus confirming various reports on the

advantages of RAAs on meal time glucose excursions [9]. Results by Plank et al. were also confirmed by a more recent meta-analysis by Rys et al. on insulin aspart (IAsp) [10], not showing a significant effect on HbA1c and PPG in T2DM subjects.

Table 1. Current available insulin analogs.

| Molecule (Trade company) | Insulin type and structure | Drug kinetics |
|-------------------------------|---|--|
| Rapid-acting | | |
| Lispro (Eli Lilly®) | Lys (B28) Pro (B29) | Beginning 10-15 min Peak 1-3 hours Duration 3-4 hours |
| Aspart (Novo Nordisk ®) | Asp (B28) | Beginning 10-15 min Peak 1-3 hours Duration 3-4 hours |
| Glulisyn (Sanofi Aventis ®) | Lys (B3) Glu (B29) | Beginning 0 – 15 min Peak 0.5 – 1.5 hours Duration 3 – 4 hours |
| Intermediate-acting | | |
| Lispro protamin (Eli Lilly ®) | Lys (B28) Pro (B29) plus protamine | Beginning 2 - 4 hours Peak 5 - 6 hours Duration 15 - 17 hours |
| Long-acting | | |
| Detemir (NovoNordisk ®) | Lys B29 (N-tetradecanoyl) des (B30) | Beginning 2 hours No peak Duration about 20 hours |
| Glargine (SanofiAventis ®) | Gli (A21) Arg (B31) Arg (B32) | Beginning 1-2 hours No peak Duration about 24 hours |
| Premixed | | |
| Different mixtures available | Premixed rapid-acting and protamine-bound analogues | Beginning 15 min Peak 0.5 - 1.2 hours Duration 13 - 16 hours |

The results of these meta-analyses may be relevant when evaluating the economic costs associated with recombinant technologies, although the possible long-term benefits of RAAs, including the potential cardiovascular advantage of specifically targeting PPG excursions [11], should also be taken into account.

Overall, different RAAs have shown a similar efficacy in reducing PPG excursions and the rate of hypoglycaemia and their mitogenic activity is comparable to that of human insulin [3, 12].

Some differences exist for the use of different RAAs in pregnancy: insulin aspart has been specifically tested in several RCTs and it has received registration for this indication; insulin lispro has been shown to be safe in several observational studies, whereas no published data on the use of glulisine in pregnant women are available yet [18-20].

3. Long-Acting Insulin Analogs

The shorter duration of action of RAAs with respect to RHI has unveiled the need of long-acting peak-less insulin preparations to guarantee basal insulinization and to avoid pre-prandial glucose increase, especially in insulin-deficient individuals [16].

Two long-acting analogs (LAAs) are currently available for clinical use (table 1). Insulin glargine results from the

addition of two arginine residues in the B chain, and the substitution of asparagine with glycine at the A21 residue (A21Gly, B31Arg, B32Arg). These modifications make glargine less soluble at physiological pH levels, and lead to the deposition of microprecipitates in the s.c. tissue, thus delaying its absorption and prolonging its duration of action [17, 18]. Detemir is a structurally modified insulin by means of a deletion of treonine on B-chain and acylation of lysine B29 with miristic acid. Detemir is soluble at a neutral pH, tends to self-association and reversibly binds to albumin, which is responsible for its slow absorption and protracted duration of action when compared to NPH. Furthermore, since detemir remains soluble once injected in s.c. tissue, this seems to reduce insulin inter- and inpatient variability [17, 19].

Numerous large, multicenter RCTs have compared NPH insulin with either insulin glargine or detemir. A meta-analysis [20] showed that LAAs are as effective as NPH in terms of glucose control in T2DM patients, although more patients in the glargine or detemir groups achieved glucose targets without nocturnal hypoglycaemia, and with higher treatment satisfaction scores [21, 22]. Recently, the SOLVE study, the largest multicenter observational trial on insulin therapy in T2DM, demonstrated that insulin detemir was effective and safe also in the “real life” setting of patients that are not usually included in the registration trials, i.e., those who start insulin therapy late, when hypoglycemic risk

is higher because of an older age and concomitant long-term complications [23].

PK and PD properties of NPH and the two available LAAs were recently compared in 18 T2DM subjects, who underwent repeatedly euglycaemic clamps. In this study, insulin glargine provided a greater metabolic activity and superior glucose control for up to 32 h, with a mean GIR0-32 h, a surrogate measure of insulin metabolic activity, that was 31% greater than NPH and 42% higher than insulin detemir [24]. However, several head-to-head studies that have compared the efficacy and safety of insulin glargine and detemir showed no significant differences with respect to glycemic control and both nocturnal and severe hypoglycemia [25]. Notably, insulin detemir was associated with more frequent twice-a-day need of use, an higher insulin dose requirement and lesser weight gain, when compared to glargine [26-29]. The reasons for the lower weight gain with insulin detemir are not completely understood, although they may be related to a reduced energy intake involving hormones regulating satiety [30].

To date, there is no specific information on the use of LAAs in pregnancy, although both LAAs are usually prescribed off-label, and large surveys showed that they are safe and well tolerated compared with human insulin [13-15].

Some concern has been recently raised regarding a major safety issue with the use of insulin glargine, i.e. that of a potentially increased cancer risk. This concern comes from some observational, mainly retrospective studies and it is especially related with the incidence of breast cancer; however, subsequent data did not report any disparity in cancer incidence between participants treated with insulin glargine and those treated with other types of insulin [31, 32]. Furthermore, the American Diabetes Association and the American Cancer Society recently published a joint consensus report that did not lead to firm conclusions on insulin therapy and cancer risk [33].

4. Premixed Insulin Analogs

Another, more convenient and largely used approach to insulin therapy is that based on “premixed” insulins, consisting of a fixed combination of NPH and RHI or RAA, in different ratios. These biphasic insulins are usually administered twice daily, before morning and evening meals.

In T2DM, against basal insulins once daily, biphasic insulin analogs twice daily seem to perform better in achieving the glucose targets and, even when compared with the more complex basal-bolus regimens, these premixed insulins are at least non-inferior. A recent systematic review, investigating the role of different insulin analogs in achieving optimal HbA1c targets in T2DM, showed that biphasic insulins ranked second, after the basal-bolus scheme [34]. Usually, side effects are no more frequent than with other insulins; more hypoglycemic episodes of low severity have been sometimes reported, but only in comparison with basal insulin [35, 36]. Although premixed insulin analogs may represent a more convenient insulin regimen, especially for

patients who need a simplified approach, the inability to separately titrate the shorter- and the longer-acting component of these formulations makes it a poorly flexible approach and greatly limits its use.

5. Novel Insulins

Despite the progress in insulin therapy made so far, the search of novel insulins with a better PD/PK profile, allowing a more convenient timing or way of administration is still ongoing, and several new products are close to reach the market. Among these new formulations, there are faster insulins, such as VIAject (Biodel Inc. Danbury, CT), with a more rapid onset of action, potentially even faster than the currently available RAAs, and others, which are aimed to ameliorate current LAAs' properties, such as BI-OD-Adjustable Basal (Biodel Inc. Danbury, CT), and BI-OD-Smart Basal, including glargine in their molecules [37-39].

The first to be available for use will be insulin degludec (Novo Nordisk), a phase 3 LAA which retains the human insulin amino acid sequence except for the deletion of ThrB30 and the addition of a 16-carbon fatty diacid attached to LysB29 via a glutamic acid spacer. It has an ultra-long (up to 96 hrs) life-time, derived from the soluble multi-hexamers formation, resulting in a continuous slow and stable release of insulin monomers from s.c. tissue [37,39,40]. Compared to basal insulin glargine, degludec has shown similar glycemic control and rate of hypoglycaemia, depending on the regimen used [48-51]. The BEGIN, Basal-Bolus Type 2, studies showed that insulin degludec was non-inferior to glargine in terms of glucose control, when both were administered once a day in a basal bolus regimen, and it was associated with a lower risk of hypoglycemia [41].

6. Expert Opinion

Many T2DM subjects will eventually need insulin therapy because of the progressive loss of beta-cell function over time. The aim of insulin treatment is to recreate insulin levels and mode of action as close as possible to the physiological profile, in order to achieve a tight glucose control, to reduce the risk of hypoglycaemia and to improve quality of patients' life.

While in T1DM it is an obligate choice, prescribing insulin therapy in T2DM patients is still problematic. Despite the potential benefits of early insulinization to preserve beta-cell function, insulin therapy is often delayed because of numerous barriers in both patients and care-givers, including the fear of hypoglycaemia and weight gain, difficulties in insulin titration, and the necessity of multiple daily glucose controls. Insulin analogs, either alone or in premixed formulations, have simplified several of these points.

However, there is no consensus on which regimen should be preferred to start insulin therapy in these patients. Actually, once daily basal insulin, added to the previously used oral agents, is the most popular regimen, and it is able to

ameliorate glucose control in the majority of T2DM patients, as demonstrated by the “treat to target” trials [21,22,28,29].

Twice a day premixed insulins [42] or a basal-plus scheme with a rapid-acting insulin at the mean meal [43] represent valid alternatives. Finally, a basal-bolus regimen may also be used in T2DM, when the more simplified ones are no longer effective [44].

In this context, Pontiroli et al [45] recently analyzed the effect of different insulin regimens and insulin analogs in T2DM during the first year of insulin treatment. This meta-analysis found that both glucose control and the risk of hypoglycaemia were primarily associated with the intensity of treatment, with final HbA1c that was higher with basal than with twice-a-day or prandial regimen, and with opposite figures for hypoglycaemia. Within basal regimens, detemir and glargine were similar to NPH in HbA1c lowering, with less hypoglycaemia, whereas within prandial regimens, RAAs were more effective than RHI on HbA1c, and induced less hypoglycaemia.

In a large meta-analysis involving >32,000 patients, Giugliano et al found that insulin analogs resulted in different success rate in achieving HbA1c targets in T2DM [34]. However, even with the best approach to insulin therapy, i.e., basal-bolus regimen, there were a considerable percentage of subjects not reaching HbA1c goals [23], although the appropriateness of an intensive glucose control in all T2DM subjects is today a highly debated issue, especially in the light of reducing cardiovascular risk [46,47].

Furthermore, several trials investigated the “durability” of glucose control with different starter insulin regimens. The DURABLE trial demonstrated a modestly longer maintenance of HbA1c levels $\leq 7\%$ in T2DM patients treated with twice daily premixed lispro formulations than with once daily glargine plus oral agents (43% vs. 35%), with an overall longer duration of glucose control in patients with lower HbA1c at baseline [48]. This study further demonstrated the benefits of early initiation of insulin therapy and, as reported in the Treating to Target in Type 2 Diabetes Trial (4-T), the relatively short duration of control in T2DM, in spite of any insulin regimen [49].

In the last decades, insulin therapy has made several steps forward and recombinant DNA technology has made available different formulations for clinical use, starting from human insulins (RHI and NPH) and coming to the current analogs, and to novel insulins that are ready to be introduced into the market.

Insulin analogs have ameliorated several critical points of insulin therapy, i.e., timing of insulin administration, flat basal profile, and hypoglycemic risk. Overall, both RAAs and LAAs seem to better perform in basal-bolus schemes, representing the insulins of choice in T1DM. In T2DM, different schemes, either with recombinant insulin or insulin analogs seem to be efficacious in targeting HbA1c, although analogs should be preferred when considering hypoglycemic risk and the opportunity to tailor treatment on patients' lifestyle.

Nevertheless, many problems persist: although improved,

the possibility to achieve an optimal plasma glucose control while avoiding hypoglycaemia is still far from being obtained in many patients; furthermore, the selection of which insulin regimen will better fit patients' needs is still challenging, not to mention the uncomfortable route of administration.

For these reasons, new insulin formulations and devices are under intensive research and it is likely that in a relatively short period of time insulin therapy will be enriched by these new opportunities, that hopefully will represent a progress on the long way to match a system that is perfectly regulated in nature, i.e. the physiological insulin secretion and action.

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