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Editorial

When should fixed ratio basal insulin/glucagon-like peptide-1 receptor agonists combination products be considered?

1. Introduction

1.1. Diabetes and combination of GLP-1 RA

Combination therapy for common chronic diseases such as diabetes and hypertension has been available for many years in the form of oral agents being combined in a variety of doses. Such combinations are more frequently used for treating hypertension but may be less popular for treating diabetes, for reasons that are unclear.

Indeed, diabetes lends itself to being suitable for such combination therapy because of the large number of medications that patients need to take, leading to difficulties with adherence and increased costs. Several medications are usually needed to address the multiple defects contributing to hyperglycemia.

Recently, the combination of two injectable therapies, basal insulin and GLP-1 receptor agonists [GLP-1RA] have become available and approved[1–5]. This is novel in that there is no other disease state in which injectable agents are combined to allow two medications to be injected at the same time. It does have the additional advantage of decreasing not just medication burden for patients but also reducing the number of injections which is greatly disliked by patients. However, there are some limitations as the ratio of the component injectables is fixed and multiple dose combination is not available as in combination pills.

1.2. Why is it difficult to achieve and maintain glycemic targets in diabetes?

The cause of failure to achieve and maintain glycemic targets is likely to be multiple and due at least in part to the complex pathophysiology of type 2 diabetes with at least eight abnormalities for which treatments are available, and the likelihood that there are even more abnormalities present. Treatment often consists of one or two medications, leaving the other pathophysiological abnormalities to continue to operate and worsen the condition.

A key abnormality in the progression of the disease is the decline in beta cell function and beta cell mass, as well as increased insulin resistance. In presence of insulin resistance insulin secretion increases as a compensatory mechanism. Beta cell function is already significantly impaired at the time of diagnosis of diabetes and the decline in function continues despite many of the treatments that are used in practice. While some treatments are known to slow some of the progression, there is currently no treatment that completely reverses it.

1.3. When would a combination of insulin and GLP-1 RA be useful in clinical practice?

The American Diabetes Association Guidelines state that all choices are acceptable when advancing therapy with selection based on cost, efficacy, side effects, particularly weight gain and hypoglycemia, as well as the complications of diabetes.[6] Following recent clinical trial evidence,[7–9] the standards of care recommended that in patients who were uncontrolled with diabetes and had established atherosclerotic cardiovascular disease, selected SGLT2 inhibitors such as empagliflozin or GLP-1RA such as liraglutide should be considered, as they have been shown to reduce events and mortality.

In clinical practice it is common to see patients on 2–3 oral agents who are very poorly controlled, appear insulin deficient with a high A1C and are obese. Such patients clearly have multiple pathophysiological defects that have not been addressed. Some of these patients may have tried other agents but discontinued due to side effects. Further complications such as CVD and CKD may be present. Insulin therapy is very appropriate in such patients' but hypoglycemia and weight gain are significant problems. Further, patients are more reluctant to start insulin.

1.4. Assessing and addressing common psychosocial barriers to injectable therapy

Patients frequently fear injections because they don't like needles and have fear of them. They consider them painful and they also have a bias against insulin because of known hypoglycemia and weight gain and adverse effects on lifestyle. They feel it may affect their relationship with family and friends and that the need for insulin represents personal failure in managing their disease. Appropriate diabetes education is needed to allay these fears and misconception.

Because of its ability to lower A1c substantially, as well as its established place in therapy patients are often started on basal insulin as the first injectable with the oral agents continued. This often improves glycemic control but many patients do not get to goal and those that do are at high risk of weight gain and hypoglycemia. This made it challenging to increase the dose of insulin further because of the risk of hypoglycemia, which is well known to occur as the basal insulin dose is up-titrated. Further, post prandial hyperglycemia is often not address and may explain a high A1c, even though fasting glucose may not be very high.

The ADA Guidelines recommend that such patients should be treated either with a rapid-acting insulin in addition to the basal insulin,

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or adding GLP-1 receptor agonists (Fig. 1). Often this results in additional injections, which patients may not accept leading to poor adherence.

2. Evidence for efficacy of a combination of GLP-1RA and insulin

Combinations of basal insulin and GLP-1RA demonstrate considerable synergy as they have complementary mechanisms of action and both are fairly powerful at lowering blood glucose (Fig. 2). However, as to which of these two is used first depends on considerations of cardiovascular disease, efficacy and cost, as per the Guidelines.

Adding a GLP-1 receptor agonist to basal insulin, has advantages over adding prandial insulin, which requires more injections and increases the risk of hypoglycemia and weight gain.[10] A pioneering randomized control study of adding exenatide twice daily injections to the treatment of patients who were receiving insulin glargine showed significant improvement in glycemic control with decrease of $HbA_1(c)$ level by 1.74% with exenatide and 1.04% with placebo (between-group difference, −0.69% [95% CI, −0.93% to −0.46%]; $p <$ .001). Although the study lasted only 30 weeks recipients in exenatide group noted with decrease in weight by 1.8 kg in contrast with weight gain with by 1.0 kg in placebo group with between-group difference, −2.7 kg (CI, −3.7 to −1.7). Also, the rate of hypoglycemia was similar between there exenatide recipient and placebo group. Further, less glucose monitoring may be needed with GLP-1RA, as compared to a regimen using prandial insulin.[10]

Thus, such a combination is a powerful injectable combination and has been shown to cause less weight gain. However, if given separately, it would result in 14 injections per week if the GLP-1RA was given daily or 8 injections a week if given weekly,[11] whereas a single injection combination could be given with 7 injections per week.

A wide variety of trials have been done demonstrating the efficacy of such a combination. The first of these was done by Buse et al., which demonstrated improved glycemic control with some degree of weight loss as opposed to weight gain, if insulin was optimized.[10]

Another study demonstrated that adding insulin to patients previously treated with a GLP-1RA also led to significant improvement in glycemic control.[12] In this 38-week study initially glucagon-like peptide 1 receptor agonists (liraglutide) was added to metformin for 12 weeks. This led to mean reduction in hemoglobin A1c by 1.3% from 7.7% in 61% of participants; with no reduction in HbA1C noted in 39% of participants (−0.6% from 8.3%). Participants who did not achieved HbA1C <7% were randomized in two groups with one group to continue with metformin and liraglutide, and to the other group insulin detemir added to the regimen with metformin/liraglutide. At week 26 further decreased in HbA1C from 7.6% at randomization by 0.5% (to 7.1%) noted in group with insulin detemir compare to 0.02% (to 7.5%) in group without insulin detemir with estimated treatment difference −0.52 [95% CI −0.68 to −0.36]; $p <$ .0001. Weight loss during initial 12 weeks of trial was 3.5 kg. Further decrease in weight observed with insulin detemir by 0.16 kg and without insulin detemir 0.95 kg. Hypoglycemia event were minimal with 0.286 and 0.029 hypoglycemia events per participant-year with and without insulin detemir (9.2 vs. 1.3%).

Several studies have demonstrated that adding a weekly GLP-1RA to basal insulin leads to as good control as adding a rapid-acting prandial insulin, but with less weight gain and hypoglycemia. A meta-analysis has demonstrated the value of adding GLP-1RA in combination with insulin[13] . Adding short-acting GLP-1 receptor agonist (Exenatide twice a day BID) to basal insulin improved postprandial glucose control by reduction of postprandial glucagon secretion, decreasing gastric emptying, and increasing glucose dependent insulin secretion in addition to improvement of fasting glycemic control provided by the basal insulin. Combination of therapy promotes weight loss and decrease in BMI, reduction in both prandial and basal insulin dose. Adverse effects reported in combination therapy as well as compliance with GLP-1 receptor agonists were very similar that reported in monotherapy treatment with GLP-1 receptor agonists.

3. Choosing the appropriate GLP-1RA to achieve patient treatment goals

Several factors need to be considered when choosing the appropriate GLP-1RA. These include biomedical factors related to the GLP-1RA, such as targeting fasting or postprandial glucose, the duration of action, reduction in body weight, and severity of side effects. In addition, psychosocial factors such as patients' ability to adhere to the treatment and cost factors become important.

Short acting GLP-1 receptor agonists demonstrate significantly better effect on postprandial glucose compared to the longer acting GLP-1 receptor agonists. Longer-acting GLP-1 receptor agonists (Liraglutide) lead to a better reduction in fasting glucose compare to the short acting GLP-1.

Some GLP-1 RAs such as Liraglutide have been shown to reduce Cardiovascular (CV) events in cardiovascular outcome trials. However, this benefit was not seen in a trial with lixisenatide. The difference may be related to a difference in the population studied and a shorter duration of the trial. Thus, it is unclear whether the benefit is a class effect, although the FDA has given a CV indication only to some of the drugs. On the other hand, in patients without Cardiovascular Disease (CVD), any of the drugs would have their known benefits on glycemic control and weight loss.

4. Fixed ratio insulin GLP-1RA injections

Two fixed ratio combinations (FRC) are currently available: insulin degludec combined with liraglutide and insulin glargine combined with lixisenatide. These FRCs have been demonstrated to have better efficacy than either component given alone, improving both fasting and postprandial glucose levels with a simplified regimen that could increase patient adherence. There are limitations, however, in that nausea remains problematic and dose titration is required.

Both FRA combinations have been available for some time, but initially were only approved in patients who failed to achieve goals with one of the components. The FDA recently approved the expanded approval of these combination injections in people with poor controlled diabetes while on oral antidiabetic medication. Thus, a fixed ratio combination can now be used as the first injectable in patients failing on oral agents.

A fixed ratio combination of insulin glargine and lixisenatide (iglarlixi) can now also be prescribed for patients uncontrolled on oral antidiabetic medicines such as metformin and/or a second antidiabetic oral therapy. Treatment with iglarlixi led to remarkable improvement in blood glucose level and hbA1C compare to insulin glargine and lixisenatide alone (−1.6%, −1.3%, −0.9, respectively with $p <$ .0001) in people with uncontrolled T2DM while on metformin and second OAD in addition to diet and exercise. Hypoglycemic episodes were almost equivalent between Insulin glargine (23.6%) and iglarlixi(25.6%). Hypoglycemic episodes were lower with lixisenatide-6.4%.

There have been several clinical trials of the insulin degludec/liraglutide combination, all demonstrating very substantial improvements in glycemic control. The DUAL I trial demonstrated that it was possible to reduce the A1c from 8.3 to 6.4%, which was not achieved with either drug used alone. In this phase 3, 26-week, open-label, randomized trial, adults with type 2 diabetes, were randomly assigned to daily injections of IDegLira, insulin degludec, or liraglutide. In 1663 adults (mean age 55 years [SD 10], HbA1c 8·3% [0·9], and BMI 31·2 kg/m^2 [4·8]) were randomly assigned, 834 to IDegLira, 414 to insulin degludec, and 415 to liraglutide. After 26 weeks, mean HbA1c had decreased by 1·9% (SD 1·1) to 6·4% (1·0) with IDegLira, by 1·4% (1·0) to 6·9% (1·1) with insulin degludec, and by 1·3% (1·1) to 7·0% (1·2) with liraglutide. IDegLira was non-inferior to insulin degludec

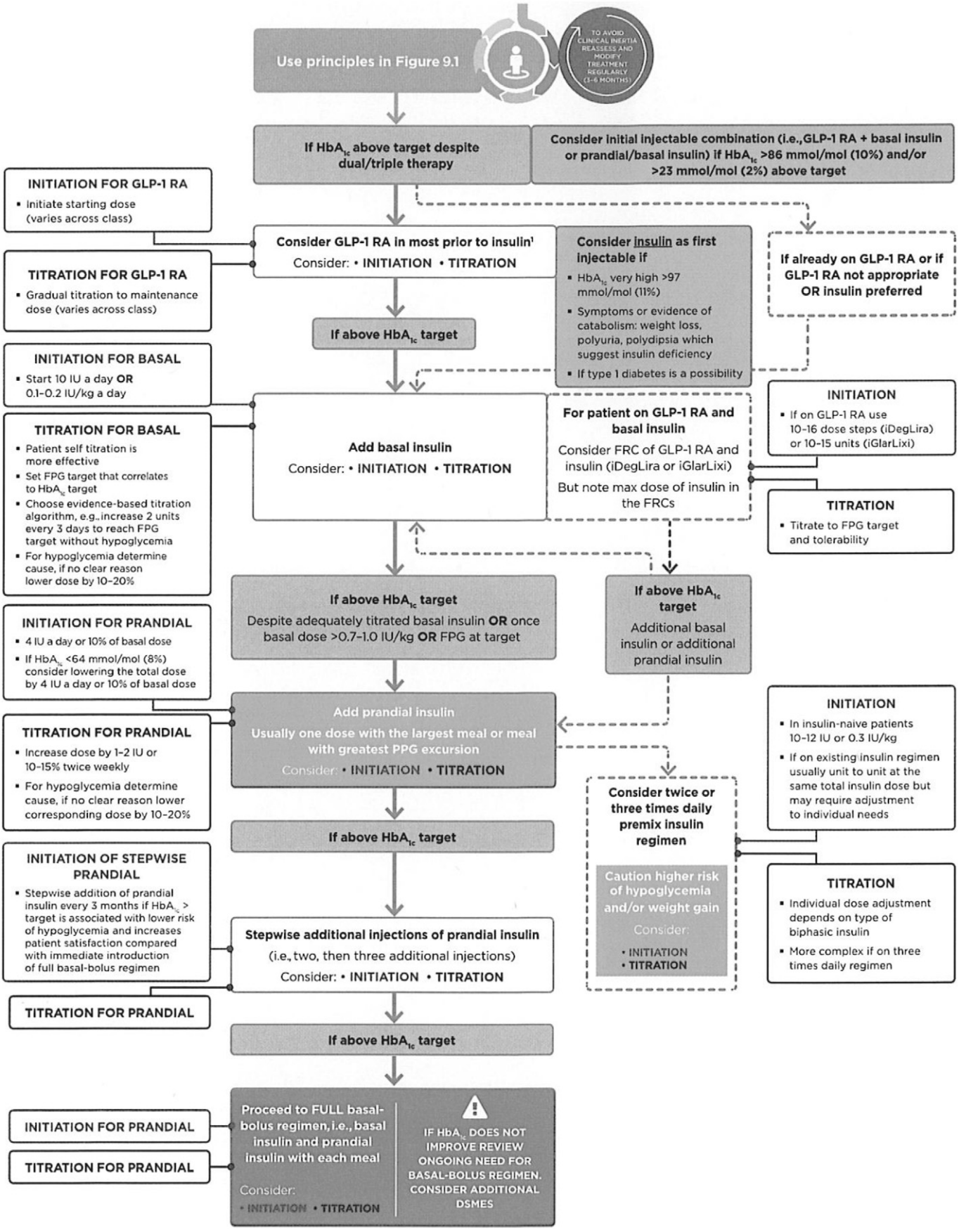

Fig. 1. Pharmacologic Approaches to Glycemic Treatment: Standards of medical Care in Diabetes – 2019, Diabetes Care 2019 Jan; 42 (Supplement 1): S90-S102. Reprinted with permission from the American Diabetes Association.

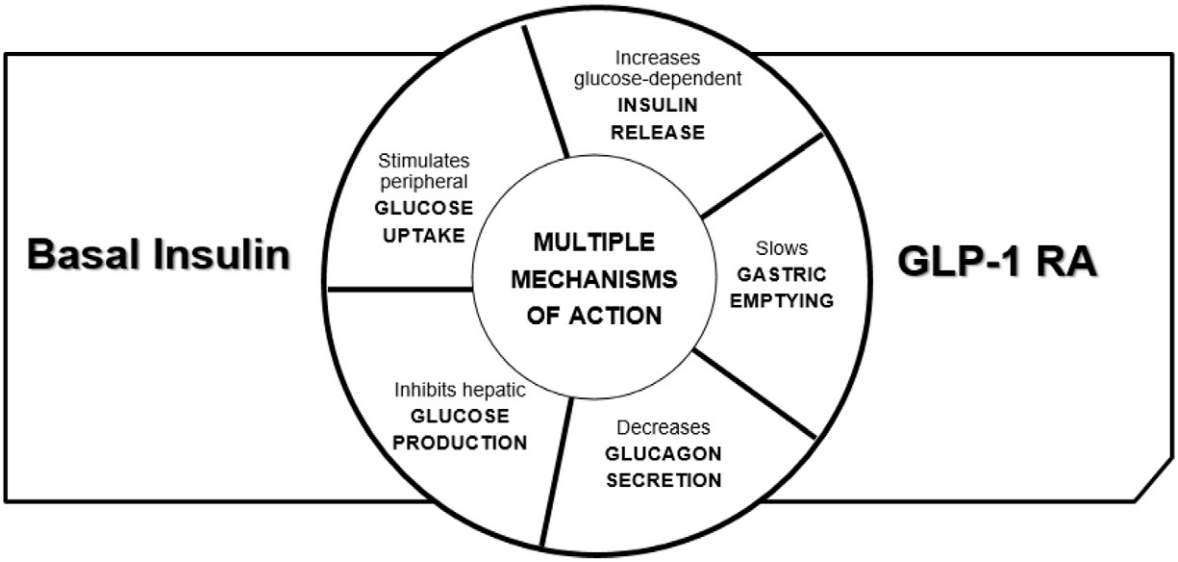

Fig. 2. Basal insulin and GLP-1 RA complementary mechanism of action.

(estimated treatment difference −0·47%, 95% CI −0·58 to −0·36, $p < 0·0001$) and superior to liraglutide (−0·64%, −0·75 to −0·53, $p < 0·0001$). IDegLira was generally well tolerated; fewer participants in the IDegLira group than in the liraglutide group reported gastrointestinal adverse events (nausea 8·8 vs 19·7%), although the insulin degludec group had the fewest participants with gastrointestinal adverse events (nausea 3·6%).

It is remarkable that the rates of nausea on the combination were much lower than that seen with liraglutide given alone, perhaps because of the slow titration that was possible. Titration is done in multiple steps based on insulin titration, rather than the 3 steps recommended when liraglutide is used alone.

Other trials have compared the combination with either insulin alone or GLP-1 alone, and demonstrated the superiority of the combination. DUAL II was a 26-week, double-blind trial, patients with type 2 diabetes on basal insulin (20–40 units) and metformin. Participants were randomized to once-daily IDegLira + metformin or IDeg + metformin with titration aiming for fasting plasma glucose between 4 and 5 mmol/L. Maximum allowed doses were 50 dose steps (equal to 50 units IDeg plus 1.8 mg liraglutide) and 50 units for degludec. A total of 413 patients were randomized (mean A1C 8.8% [73 mmol/mol]; BMI 33.7 kg/m^2). IDeg dose, alone or as part of IDegLira, was equivalent (45 units). A1C decreased by 1.9% with IDegLira and by 0.9% with IDeg (treatment difference −1.1%). Mean weight reduction with IDegLira was 2.7 kg vs. no weight change with Ideg. Thus, lack of weight gain is another important advantage of the combination.

Similarly, the combination of insulin glargine and lixisenatide has been shown to be effective in many trials. The first of these demonstrated that it was possible to lower A1c from above 8 to 6.3%. While good control was obtained also by optimizing glargine in that study, it led to more weight gain and hypoglycemia. Further glucose profiles demonstrate very good postprandial glucose control with such a combination. Studies also confirm lower rates of nausea than with lixisenatide alone, very similar to what has been observed in the fixed ratio combination of degludec and liraglutide.

Similarly, Rosenstock et al. assessed the efficacy and safety of iglarlixi, a fixed-ratio, titratable, combination of 2 units insulin glargine (Gla-100) and 1 μg lixisenatide administered once daily via a single pen, versus Gla-100 in insulin-naïve type 2 diabetes on metformin. Participants were randomized to once-daily iglarlixi or Gla-100 for 24 weeks, while continuing metformin. Iglarlixi and Gla-100 were started at 10 units/5 μg and 10 units, respectively, and titrated based on the Gla-100 requirement according to fasting plasma glucose levels. At week 24, mean HbA1c was reduced from 8.0% at baseline to 6.3% and 6.5% with iglarlixi and Gla-100, respectively. Iglarlixi improved 2-h postmeal plasma glucose versus Gla-100. Body weight was reduced with iglarlixi (−1 kg) and increased with Gla-100 (+0.5 kg;), with no increase in hypoglycemic events and the incidence of nausea (7.5%) and vomiting (2.5%) was low with iglarlixi. Thus, iglarlixi achieved statistically significant reductions to near-normal HbA1c levels with weight loss and no increased hypoglycemic risk, compared with insulin glargine alone, and a low incidence of gastrointestinal adverse events in type 2 diabetes inadequately controlled on metformin. The approved FRC iglarlixi however, consists of a 100/ 30 ration of glargine and lixisenatide.

5. Practice considerations for GLP-1RA and basal insulin combinations

Is there a difference between the two FR combinations? No head-to-head comparison has been done with the FRCs and therefore it is not possible to make recommendations between the two for glycemic control alone. However, liraglutide has been approved for treatment of atherosclerotic cardiovascular disease, whereas Lixisenatide does not have this indication. The maximum dose of insulin in IDegLira is 50 units, whereas it is 60 units in iGlarLixi, perhaps making the latter more suitable for patients who need higher doses of insulin.

5.1. Should an FRC be the first injectable?

As discussed above, disease progression leads to a large proportion of patients on oral agents failing to meet goals over time. When injection becomes inevitable, it may seem appropriate to use such a combination, which could lead to not only better glycemic control but with less side effects (less weight gain than insulin alone and less nausea/ vomiting than GLP-1 alone). Such a paradigm could eventually lead to FRCs becoming the first injectable of choice for most patients with type 2 diabetes.

The combination has to be administered within 1 h of the first meal of the day at the same time. Starting dose of the combination of insulin glargine and lixisenatide injection 100 units/mL and 33 μg/mL depends on the patient sensitivity and patient's current dose of long acting insulin. 15 units/5 μg dose is the initial dose in patient naïve to insulin and patient whose current basal insulin dose is <30 units a day. 30 units/10 μg iGlarLixi recommended in patients who are on higher dose of basal insulin −30-60 units /day. The iGlarLixi dose should be adjusted by 2–4 units weekly based on patients' blood glucose results, The maximum daily dose of 60 units insulin glargine and lixisenatide 20 μg.

6. Summary and use in practice

In patients with long standing type 2 diabetes adjustment to medical management is necessary due to deterioration in glycemic control.

Basal insulin, which can be initiated at various stages of type 2 diabetes, is very effective at reducing fasting plasma glucose (FPG). Although titratable, the higher the dose the higher the risk of hypoglycemia and weight gain this limits our ability to achieve tight glycemic control without adverse effects.

Adding prandial insulin and up titration basal insulin is required to achieve glycemic control. Increasing the insulin dose raise the risk for hypoglycemia, and can lead to increase in weight/BMI, worsening weight related comorbidities. Hypoglycemia also increase the risk of macrovascular and microvascular events. Avoidance of hypoglycemic episodes can lead to poor compliance with higher insulin doses.

On the other hand, GLP-1 RAs can also be used at various stages of type 2 diabetes and they have a complementary mechanism of action to basal insulin. A co-formulation of basal insulin and GLP-1 has many benefits. They target multiple abnormalities in the pathophysiology of diabetes and address both fasting and postprandial glucose with no increased risk in hypoglycemia.

They allow the patient to address many aspects of the pathophysiology of hyperglycemia with one single daily injection which may improve compliance and adherence with the therapy. Combination therapy with slow titration showed improvement in glycemic control, less hypoglycemic episodes, and less GI adverse effect of GLP-1 receptor agonists.

Finally, other dose combinations (different fixed ratios) may be needed, particularly for patients who need higher doses of insulin and should be evaluated in clinical trials.

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