Insulin and glucagon-like peptide receptor agonist (GLP 1 RA) combinations
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Abstract
This review analyses a recent advance in diabetes pharmacotherapeutics: the combination of insulin and glucagon-like peptide 1 receptor agonists (GLP 1 RA). It describes the rationale for such a combination, and discusses the impact of such therapy on glycaemic control. The paper also assesses other benefits of the combination, and provides a practical framework for pragmatic, rational use of this treatment.

Keywords: Glucagon-like peptide, Glycaemic control.

Introduction
Our current understanding of the pathophysiology of diabetes mellitus has expanded significantly since modern research began in this field. From the earlier, simplistic, single etiopathology of insulinopenia, we now acknowledge multiple pathophysiological factors that operate in this syndrome. These mechanisms have collectively been named as the 'Ominous Octet', and as the 'Dirty Dozen'. This development in biochemistry has led to universal acceptance of combination therapy in type 2 diabetes mellitus. Combinations of oral anti-diabetic drugs with each other, and with insulin, are accepted in therapy now. While the ADA -EASD and IDF suggest combination therapy as a second line treatment step, the American Association of Clinical Endocrinologists (AACE) promotes use of dual and triple combination therapy, if HbA1c is above 7.5% and 9.0% at presentation respectively.3-5

In this new therapeutic milieu, combinations of injectable drugs are now being accepted as well. Regimes such as basal insulin + GLP1RA are supported by evidence now. Development of ‘fixed ratio combinations’, viz, insulin degludec + liraglutide, and insulin glargine + lixisenatide, in premixed co-formulations, are underway as well.6,7

The Rationale of Combination
While basal insulin and GLP 1 RA are effective, and useful, molecules for the control of hyperglycaemia, they do have limitations. These limitations, which occur because of the unique pharmacological properties of these drugs, can be overcome by combining the two injectables.8 The rationale behind such a combination is listed in Table-1.

Methods of Combination
GLP1RA can be added to preexisting basal insulin therapy, as an intensification regime of basal insulin failure occurs. (Table-2) Basal insulin failure can be defined as inability to achieve pre-decided target glycaemic controls, after optimization of lifestyle modification measures and maximal titration of basal dose, beyond which unacceptable hypoglycaemia will occur.9

Basal insulin can also be added to supplement the effect of pre-existing GLP1RA, in persons who do not achieve glycaemic targets with this therapy alone.10 While the term ‘failure’ is used for inadequate response to basal insulin, the word ‘non responder’ is preferred to describe suboptimal results with GLP1RA therapy. Basal insulin and GLP1RA can be started in injection-naïve persons as a combination. While currently, a ‘loose combination’ of two separate drugs has to be prescribed, premixed co-formulations of basal insulin and GLP1RA are in advanced stages of development.6

Addition of Glp1 RA to Insulin
Addition of exenatide to insulin has been found to achieve an additional benefit of 0.66% to 1.74% in various

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Table-1: Complementary action of basal insulin and glucagon-like peptide 1 receptor agonists (GLP 1 RA).

<table>
<thead>
<tr>
<th></th>
<th>Basal insulin</th>
<th>GLP 1 RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of administration</td>
<td>Subcutaneous</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>Frequency of Dosage</td>
<td>Once/twice daily</td>
<td>Once/twice daily</td>
</tr>
<tr>
<td>Primary action</td>
<td>On fasting glycaemia</td>
<td>On post prandial glycaemia</td>
</tr>
<tr>
<td>Effect on weight</td>
<td>Weight neutral or weight Gain</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>Low risk</td>
<td>Very low risk</td>
</tr>
<tr>
<td>Effect Synergistic</td>
<td>Beta cell sparing</td>
<td>Insulin sparing</td>
</tr>
</tbody>
</table>

Table-2: Combination of basal insulin and GLP1RA.

- GLP1RA intensification, after basal insulin failure
- Insulin intensification, after GLP1RA, monotherapy non response
- GLP1RA + basal insulin dual combination at onset
In a retrospective study, the HbA1c reduction of 0.66% (from a baseline of 8.05%) was maintained for 27 months, in spite of the fact that roughly 70% of the subjects had duration of diabetes of more than 10 years. In a prospective study, exenatide showed insulin-sparing effect of 7 units.

Similar results have been noted with liraglutide, which has produced extra HbA1c reductions of 1.0 to 1.4% as add-on to preexisting basal insulin therapy in various studies. A 28% reduction in insulin requirement has been demonstrated in a 12 week long observational study. Lixisenatide, too, has been shown to reduce HbA1c and other glycaemic parameters when added to failing basal insulin treatment. The relatively shorter duration of action of lixisensatide may explain its effective targeting of postprandial hyperglycaemia.

GLP1RA have been shown to be an effective alternative to intensification of insulin therapy by adding rapid acting insulin. Addition of albiglutide was found to be equally effective, in a 30mg once weekly dose) to insulin lispro, when added to patients treated with a combination of basal insulin and oral insulin sensitizers. Thus, there is evidence to support addition of GLP1RA as an intensification strategy for basal insulin failure.

Addition of Insulin to GLP1RA

GLP1RA are now recommended earlier on in the natural history of diabetes. With this style of use, it makes sense to understand whether changing GLP1RA to insulin, or adding insulin to GLP1RA.

Studies have shown that adding glargine to exenatide, or detemir to liraglutide, helps in reducing HbA1c by an extra 0.51% to 1.40%, as compared to addition of placebo. This may be an equally useful treatment strategy to achieve and maintain glycaemic goals.

Effect on Body Weight

The GLP1RA-insulin combination therapy helps reduce weight in two ways: the direct weight-reducing effect of GLP1RA, and the weight gain prevented by the reduction in insulin dose made possible by the combination. Consistent results related to weight loss has been reported by various authors.

Effect on Insulin Dose

GLP1RA addition to insulin allows for significant reduction in insulin dose, requirement ranging from 15% to 63%. The insulin sparing effect, however, is often not absolute. Complete discontinuation of basal insulin therapy, upon addition of GLP1RA, may lead to a worsening of glycaemic control, and precipitate severe hyperglycaemic episodes.

Effect of Hypoglycaemia

GLP1RA may reduce the risk of hyperglycaemia. This is mediated by their dual action upon the beta cells and alpha cells; GLP1RA increases this sensitivity of alpha cells, allowing them to secrete glucagon when glucose levels are falling, thus effectively preventing severe hyperglycaemia. This increase in sensitivity also reduces glucagon secretion after exposure to glucose loads, thus contributing to glycaemic control overall.

Pleiotropic Benefits

GLP1RA — insulin combination use is associated with multiple pleiotropic benefits, including reduction in blood pressure, body weight and lipid levels. These cardiovascular-friendly attributes suggest a role for this combination in persons at risk of cardiovascular disease.

Side Effects and Limitations

This combination suffers from the same side effects and limitations that GLP1RA have. Transient nausea vomiting may occur, albeit to a much lesser degree with liraglutide. These effects, including loss of appetite, must be explained to the patient in advance, as an integral part of the drug’s action.

Exenatide is not recommended for patients with severe renal impairment (creatinine clearance <30 ml/min), while liraglutide should be used with caution.

Pragmatic Approach

Current guidelines do not prohibit the use of GLP1RA-insulin as combination therapy. In fact, all guidelines allow its use at second line or third line therapy. However, no guidance is available to suggest when this combination should be used in preference to other intensification options, such as premixed insulin or basal-bolus insulin. GLP1RA - insulin combination will be the regime of choice in:

1. Persons not responding to GLP1RA alone with high fasting glucose, and relatively well controlled postprandial hyperglycaemia; in spite of maximally tolerated doses of metformin.

2. Persons with basal insulin failure, unable to achieve HbA1C targets, with high postprandial glucose values; and an adverse cardiovascular risk profile (overweight/obese, dyslipidaemia, hypertension).

3. Persons with adverse gastrointestinal symptoms on GLP1 RA, requesting reduction in dose of the drug.

4. Persons with increased appetite or weight gain while on basal insulin therapy.
5. Persons with high entry level HbA1c, who may be unable to reach target HbA1c with monotherapy, in the opinion of the treating physicians.

Conclusion
The GLP1RA — insulin combination represents a major advancement in diabetes pharmaco-therapeutics. Based upon sound patho-physiological principles, this combination offers efficacy with safety and tolerability.

References