

Placing Incretin-Based Therapy In Type 2 Diabetes Mellitus: Whom To Prescribe To?

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Abstract

Many reviews and articles have been written regarding the utility of novel incretin-based therapies such as DPP(IV) inhibitors and GLP-1 analogues. Few authors, however, provide practical guidance regarding the actual placement of incretin-based therapy in diabetes care. This review seeks to highlight the limitations of traditional therapy, the advantages of incretin-based treatment, and the placement of this novel modality in type 2 diabetes mellitus.

LIMITATIONS OF CONVENTIONAL ORAL HYPOGLYCEMICS

While the range of conventional OHAs has increased considerably, providing greater choice to the family practitioner, traditional drug therapy still suffers from many limitations (1,2,3).

The natural history of diabetes is characterized by gradual, progressive decline in β -cell function. The existing drugs do nothing to arrest this decline, or to improve β -cell function or mass. The sulfonylureas, in fact, tend to worsen the situation by “whipping” the β -cell and causing apoptosis.

While it is understood that the pathophysiology of diabetes is multifaceted, most conventional OHAs have a unfocused mechanism of action. Some drugs act only on fasting glycemia, while others target postprandial glycemia alone. Because of this, a combination of drugs is needed to achieve adequate control.

The complexity of these drugs, difficult dose titrations and their combinations make it difficult for practitioners to prescribe appropriate doses of these drugs. The confusing posology, times of administration and drug interactions make the use of conventional OHAs a challenge for busy doctors.

The complexity of these drugs daunts patients as well, who respond by reducing compliance. The high index of intrusion with certain drugs, which have to be given 30 minutes before meals (sulfonylureas), chewed immediately before meals (α -glucosidase inhibitors), or taken after meals (metformin),

makes it difficult for patients to follow well-meaning advice.

For patients and physicians who are able to take these drugs, the list of limitations continues.

Most drugs are linked to hypoglycemia (sulfonylureas, meglitinides) and weight gain (sulfonylureas, thiazolidinediones). These major adverse effects limit the safety and tolerability of these classes of drugs.

Other side effects such as gastrointestinal symptoms limit the tolerability and uses of metformin and α -glucosidase inhibitors. Edema, osteoporosis and congestive cardiac failure are unwanted side effects which limit the usage of thiazolidinediones.

Most traditional OHAs have a limited spectrum of usage. Metformin, for example, is contraindicated in renal failure, hepatic failure, sepsis, hypoxic states, and unstable cardiac states. Sulfonylureas are contraindicated in renal failure, while voglibose is unsafe in hepatic failure.

These limitations, i.e., the inability to address β -cell decline, the lack of a multifaceted mechanism of action, side effects such as weight gain and hypoglycemia, adverse effects on gastrointestinal, bone and cardiovascular health, a limited spectrum of use, various contraindications and drug interactions, point to the need for newer drugs.

Difficulties in posology/dose titration and administration, a high index of intrusion with some drugs, and the high complexity of combination regimes limit the acceptance of

conventional OHAs.

This leads to sub optimal compliance/adherence to prescribed drug therapy, and causes sub optimal therapeutic outcome.

ADVANTAGES OF INCRETIN-BASED THERAPY

Many of the limiting factors mentioned above can be overcome by a novel group of drugs based on the incretin effect. The details of the incretin axis, its physiology, and the drugs based on it have been discussed earlier by the author (4,5,6).

Incretin-based drugs preserve B-cell mass and function in animal models. They have a multifaceted mechanism of action, targeting the incretin axis, the B cell and the A cell.

They are easy to use, as they are characterized by fixed doses and flexibility in time of administration (except exenatide).

The glucose-dependent mechanism of action, and the resultant lack of hypoglycaemia, is a major advantage which increases the safety of these drugs, while maintaining efficacy.

Weight loss with liraglutide and exenatide, and lack of weight gain with DPP(IV) inhibitors is another factor which encourages use of this class of drugs.

The lack of other major side effects such as edema and GI disturbance with DPP(IV) inhibitor is another advantage. The incretin-based therapies can be used in mild-moderate renal failure with appropriate dose adjustments, and can be given to elderly patients.

PLACE OF INCRETIN-BASED THERAPY

The rationale for using incretin-based therapy can be listed as:

to achieve efficacy of treatment

to ensure safety of treatment

to provide tolerability of treatment

Incretin-based therapy can be used as a

Substitute for other OHAs

Add-on to other OHAs

Substitute for insulin??

Add-on to insulin

This mode of therapy can also be used in special situations such as:

Cardiovascular disease with diabetes

macrovascular disease

congestive cardiac failure

diabetic cardiomyopathy

renal failure

diabetic diarrhea

the elderly

impaired glucose tolerance

obesity

The different methods of using incretin-based therapy have been studied for all available drugs.

The evidence in favour of using DPP (IV) inhibitors or GLP-1 analogues as substitute for other OHAs, or as add-on to them, is robust (7,8,9).

Vildagliptin, saxagliptin and sitagliptin have been studied as monotherapy and found to reduce HbA1c effectively, with minimal adverse effects. Liraglutide and Exenatide can also be used as monotherapy in uncontrolled diabetes mellitus.

These drugs can also be used as add-on therapy in patients taking metformin, pioglitazone/rosiglitazone or glimeperide.

The addition of incretin-based therapy to pre-existing oral therapy leads to improvement in HbA1c, without major adverse effects.

Equally robust is the evidence in favour of adding DPP (IV) inhibitors to insulin.

Vildagliptin, saxagliptin and sitagliptin can be added to pre-existing insulin therapy.

However, there are no studies yet to support the use of GLP-1 analogues in combination with insulin. It must be noted that anecdotal evidence is available, to support this method of use.

There is no rationale in using DPP (IV) inhibitors or GLP-1 analogues as a substitute for insulin therapy and leading endocrinologists caution against this.

Incretin-based therapy may be useful in impaired glucose tolerance, as it does not cause hypoglycemia.

It may also be of special benefit in cardiovascular disease, because of its pleiotropic effects on the vascular and myocardium.

DPP (IV) inhibitors can be used safely in mild renal failure, with appropriate dose adjustment. Both DPP (IV) inhibitors and GLP-1 analogues might have beneficial effects in diabetic diarrhea, as they slow gastric emptying,

Incretin-based therapy seems to be more effective in elderly patients, who also benefit from the ease of administration, and favorable safety/tolerability profile of these drugs.

There is also a rationale for using GLP-1 analogues in obesity, and all incretin-based therapies in impaired glucose tolerance. These indications are still under investigation.

POSODOLOGY

The advent of incretin-based treatment has marked a paradigm shift in the posology of anti-diabetic drug therapy. Traditional treatment, whether oral or injectable, is characterized by complex dose titration regimens, making it difficult for general practitioners to use these drugs safely.

Incretin-based drugs, on the other hand, have fixed doses, with simple dose titration to be done for renally-impaired patients. This makes it easier for physicians to use and prescribe.

SIDE EFFECTS

Exenatide use is associated with a high incidence of nausea and vomiting. This side effect is seen less often with liraglutide, and is usually transient.

The (DPP IV) inhibitors do not exhibit gastrointestinal side effects. Commonly noticed adverse events are upper respiratory infection and headache.

In general, the tolerability and safety profile of liraglutide and DPP (IV) inhibitors is good.

CONTRAINDICATIONS/ LIMITATIONS

Appropriate use of incretin-based therapies implies that one should be aware of their limitations, risks contraindications.

Incretin-based treatment is contraindicated in type 1 diabetes, in ketonuria, in pregnancy and lactation. Sitagliptin should be avoided in severe renal failure while vildagliptin should not be given in hepatic failure. Patient with

gastrointestinal autonomic neuropathy in the form of gastroparesis may experience worsening of symptoms.

ETHNOPHARMACOLOGY

Recent data has highlighted the differences in response of various ethnic groups to anti-diabetic medications, increasing interest in ethnopharmacology of diabetes. Racial differences have been noted in GLP-1 levels of African Americans and Caucasians (10,11). Anecdotal evidence is available about the higher sensitivity of Asian patients to incretin-based therapy. While no data is available on GLP-1 levels in Asian people, research on this aspect of ethnopharmacology should reveal interesting results.

CONCLUSION

Incretin-based therapy represents a major breakthrough in the management of type 2 diabetes mellitus. Appropriate use of these drugs, placing them in the correct clinical settings, will help patients achieve effective glycemic control, and enjoy potential pleiotropic benefits, in a safe and well tolerated manner.

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