Review Article

Intensifying treatment for T2DM after oral therapy failure : GLP-1RA as the first injectable therapy

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Since the past one decade the management of type 2 diabetes mellitus (T2DM) has evolved significantly with the addition of newer antidiabetic agents like DPP4 inhibitors, GLP-1 RAs and SGLT2 inhibitors. Among these, GLP-1 RAs offer advantages like good HbA1c reduction, weight reduction, practically no hypoglycemia, cardiovascular benefits and convenient dosing with some selected agents which can further aid in improving compliance thereby helping patients in achieving the desired glycemic goals. GLP-1 RAs are recommended by all the major guidelines across the T2DM management spectrum and are an important first injectable option after oral therapy failure. This review summarizes the data available on the usage of GLP-1 RA and their important role in the management of T2DM as a first injectable therapy.

[*J Indian Med Assoc* 2019; **117(11):** 19-22]

Key words **: GLP-1RA, dulaglutide, AWARD trial.**

Glycemic Control and Clinical Inertia in T2DM :

Type 2 diabetes mellitus (T2DM) is associated with some complex pathophysiological mechanisms contributing to hyperglycemia. To target these pathophysiological defects, different antihyperglycemic agents have been developed[1]. The response to these antihyperglycemic agents varies greatly depending on their mechanism of action[2]. Traditionally, metformin is the undisputed first line AHA in the management of T2DM. After metformin monotherapy failure several AHAs are available either oral or as injectable options for treatment intensification[2]. In the last one decade, the management of T2DM has evolved with the introduction of newer AHAs like dipeptidyl peptidase 4 (DPP4) inhibitors, glucagon like peptide-1 receptor agonists (GLP-1 RA) and sodium glucose cotransporter 2 (SGLT2) inhibitors[3]. The guidelines for management of T2DM has also evolved based on the benefits seen with some of these newer AHAs in their respective cardiovascular outcome trials (CVOTs)[4].

Despite the availability of these newer and improved AHAs, T2DM patients often experience prolonged periods of suboptimal glycemic control[5,6]. According to the ICMR-INDIAB study, majority of Indian T2DM patients are sub optimally controlled with an average HbA1c hovering around 8%[7]. Typically, patients with T2DM spend approximately 6 years with an HbA1c of more than 8%. In T2DM patients who were on 3 oral AHAs and with HbA1c ≥8%, the time to additional therapy was 1.6 years for additional oral AHA and more than 6 years for insulin. Thus, there are significant delays in treatment intensification in patients with T2DM despite suboptimal glycemic control with a substantial proportion of patients experiencing poor glycemic control for several years before intensification with oral AHAs and insulin[6]. In terms of using insulin, physicians may be reluctant due to a belief about risk to patients with and without comorbidities, fear of hypoglycemia, excess weight gain, deranged quality of life, beliefs about patient competence and available resources[8,9]. These patient related factors further add to the clinical inertia compromising the ability of reaching the target HbA1c[10]. Hence, after oral therapy failure, there is a need for a noninsulin injectable AHA which can be beneficial in terms of achieving good glycemic control but mitigating the fears about safety and tolerability.

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Overview of Incretin-based Therapies and GLP-1RAs :

Agents in the GLP-1RA class are incretin-based therapies which are different from the DPP4 inhibitors in terms of mechanism of action mimicking the role of endogenous GLP-1, stimulating pancreatic islet cells to release insulin in response to glucose ingestion[11]. The key characteristics of incretin based therapies are illustrated in Table 1.

GLP-1RAs also inhibit glucagon release and result in good weight reduction by reducing patients' appetites due

Table 1 — *Comparison of incretin-based therapies*[3,12]

Properties/Effect	GLP-1 RAs	DPP-4 inhibitors
Route of Administration	Subcutaneous injection	Oral
Dosing	Once daily, twice daily, or once weekly depending on the agent used	Once or twice daily depending on the agent used
Glucose dependent stimulation of insulin secretion	Yes	Yes
Glucose dependent reduction of increased glucagon	Yes	Yes
HbA1c reduction	-1.1% to -1.6%	-0.6% to -1.1%
Gastric emptying	Slows gastric emptying	No effect
Food intake	Decreased	No effect
Effect on body weight	Weight loss	Weight neutral
Hypoglycemia	Nil (except when combined with insulin or sulfonylureas)	Nil (except when combined with insulin or sulfonylureas)
Adverse Effects	Nausea, vomiting, risk of pancreatitis?	Good tolerance, respiratory infections? Risk of pancreatitis?

to their ability to delay gastric emptying[12,13]. Worldwide several brands and formulations of GLP-1RAs are approved to treat T2DM, all of which have slightly different pharmacokinetic properties, clinical effects and methods of administration[14]. GLP-1RAs are broadly classified as long-acting and short-acting formulations. In India, currently there are three GLP-1 RA formulations available for clinical use (Table 2).

Short Acting GLP-1RAs :

The glycemic control achieved with short-acting GLP-1RAs is primarily driven by reductions in postprandial glucose which contributes to overall HbA1c levels[13,16]. Among the short acting GLP-1RAs,lixisenatide has been evaluated in the Get-Goal program of randomized, controlled, phase 3 clinical trialsas an intensification to basal insulin. The Get-Goal clinical trials involved different comparators including placebo, rapid acting insulin, or another GLP-1RA.The results from these studies demonstrated that once daily lixisenatide was noninferior to once or thrice daily rapid acting insulinin reducing HbA1c levels. However, lixisenatide was superior to rapid acting insulin as an add-on in achieving weight reduction[17]. According to a meta-analysis of 5 trials comparing lixisenatide vs rapid acting insulin, significantly greater proportion of patients taking lixisenatide (29%) achieved the composite end point of an HbA1c <7%, no weight gain, and no incidents of hypoglycemia as compared to patients taking rapid acting insulin (15%) (P =0.0046)[18].

Long Acting GLP-1RAs :

When it comes to lowering fasting plasma glucose levels, long-acting GLP-1RAs predominantly more effective. However, there are studies involving long-acting liraglutide and dulaglutide demonstratingreductions in postprandial glucose levels from baseline[16,19]. Dulaglutide is a once weekly GLP-1RA which is well studied in the comprehensive clinical trial programme called AWARD (Assessment of Weekly Administration of LY2189265 in Diabetes)[14]. In one such AWARD 2 randomised, 78-week, open-label study the effects of dulaglutide *versus* insulin glargine on glycaemic control was compared in adult T2DM patients uncontrolled on metformin and glimepiride. In this study, dulaglutide 1.5 mg was superior to insulin glargine and dulaglutide 0.75 mg was non-inferior to insulin glargine as measured by change in HbA1c. Throughout the trial, a higher percentage of patients on both dulaglutide doses achieved HbA1c targets of ≤6.5% and <7.0% than those on insulin glargine. At 52 weeks, the mean reduction in fasting serum glucosefrom baseline was 16 mg/dl, 27 mg/dl, and 32 mg/dl for dulaglutide 0.75 mg, dulaglutide 1.5 mg, and insulin glargine, respectively. At the 52-week primary endpoint, a greater decrease from baseline for overall daily mean PPG for dulaglutide 1.5 mg was seen. At week 52, patients receiving dulaglutide 1.5 mg achieved a mean weight loss of 1.9 kg, patients receiving dulaglutide 0.75 mg achieved a mean weight loss of 1.3 kg, and patients receiving insulin

Table 2 — *Overview of GLP-1RAs available in India*[14,15]

Properties	Dulaglutide	Liraglutide	Lixisenatide
Half life	4.7 days	13 hours	3 hours
Dosing frequency	Once weekly	Once daily	Once daily
Dose	**Monotherapy :** 0.75 mg once weekly **Add-on therapy :** 1.5 mg once weekly	1.2–1.8 mg daily	20 µg daily
Administration in relation to meals	At any time, without regard to meals	At any time, without regard to meals	Should be administered within 60 min before any meal
Single dose pen	Yes	No	No
Dose selection required	No	Yes	Yes
Dose titration	No	Yes	Yes
Needle attachment required	No. Pre-attached hidden needle	Yes. Needles ars not included	Yes. Needles are not included
Need to prime device before use	No	Yes	Yes
Automatic dose administration	Yes	No	No

glargine experienced a mean weight gain of 1.4 kg. At 78 weeks, overall safety and tolerability profiles of dulaglutide were consistent with the GLP-1 RA class, including a higher incidence of GI-related AEs with Dulaglutide than with insulin glargine. Mean rates of total and nocturnal hypoglycemia were lower compared with glargine for both dulaglutide groups[19].

In T2DM patients failing to achieve the desired HbA1c targets with triple therapy or for patients with an HbA1c of ≥10% at diagnosis, rapid-acting insulinis commonly used to augment basal insulin[2]. However, with the introduction of GLP-1RAs the treating physicians has now got an additional option for therapy intensification. According to various clinical trials GLP-1RAs have been demonstrated to be as efficacious as postprandial rapid acting insulinin improving glycemic control in patients with an inadequate response to basal insulin.The risks and benefits of RAIs and GLP-1RAs, along with treatment goals and patient preference, should be considered whenever therapy intensification is required.2In the AWARD-4 study which was a randomised, 52-week, open-label comparison of the effects of dulaglutide *versus* insulin glargine, each in combination with insulin lispro, the combination of dulaglutide and prandial insulin lispro was associated with a significantly greater improvement in glycaemic control than combined insulin glargine and prandial insulin lispro with lower risk of total and nocturnal hypoglycemia[20].

Adverse Events Associated with GLP-1RA :

None of the currently available AHAs are immune to adverse effects. Similarly, the GLP-1RAs are also associated with adverse events especially of gastrointestinal origin consisting of nausea, vomiting, and diarrhea. T2DM patients taking GLP-1RA may experience nausea, which typically resolves within the first week and rarely leads to treatment discontinuation[21]. Some patients develop upper respiratory infection or injection-site reactions[22]. It is important to inform and educate the patients about the adverse events and proper counseling should be provided as to how they can overcome and continue with the therapy. Some of the dietary measures to relieve nausea include eating small amounts of food every few hours rather than 2-3 large meals per day, avoiding greasy, fried and spicy foods[23,24].

The drug discontinuation rates due to adverse events in some of the long-term studies of GLP-1RAs have ranged from 4% to 21%[6]. Some cases of pancreatitis have been reported with GLP-1RA use, but the causality association has not yet been established[22]. When choosing a GLP-1RA the method of administration (once daily vs once weekly) delivery device, ease of use and overall safety profile must be weighed considering the patient perspective.

Role of GLP-1RA as the First Injectable Therapy :

Despite being highly effective, 43% to 50% of patients receiving basal insulin are unable to achieve the desired glycemic targets. In patients who do achieve the optimum glycemic control with basal insulin, the progression of disease compromises its effectiveness, and therefore additional AHA needs to be added[25]. The American Diabetes Association (ADA) guidelines recommend basal insulin in the presence of severe hyperglycemia, especially if symptoms are present or any catabolic features like weight loss or ketosis are present. However, considering the overall glycemic, extraglycemic and cardiovascular benefits, the ADA 2019 guidelines now recommend GLP-1RA as the first-line injectable treatment ahead of insulin for most T2DM patients who need greater efficacy of an injectable medication[2].

The guidelines also emphasize the use of GLP-1RAs with demonstrated cardiovascular disease benefit like liraglutide, dulaglutideafter metformin monotherapy failure as part of the antihyperglycemic regimen in T2DM patients with established atherosclerotic cardiovasculardisease. The GLP-1RAs are also one of the recommended options after metformin in T2DM patients without ASCVD but at risk of hypoglycemia and in those intending to achieve weight reduction[2]. Liraglutide is FDA approved to reduce the risk of MACE in adults with type 2 diabetes and established CVD; liraglutide and dulaglutide showed superiority for MACE outcomes in large CVOTs; semaglutide showed superiority for MACE outcomes in a safety CVOT however, there was also an increased risk of diabetic retinopathy[26-28]. The results from these CVOTs were primarily in patients with known ASCVD although there was consistent benefit in the dulaglutide trial in patients with and without established ASCVD[28].

Most of the available AHAs including insulin are predominantly cleared by the kidneys and hence either require dose modification or are contraindicated in T2DM patients with chronic kidney disease (CKD)[29]. GLP-1RAs like dulaglutide are not cleared by kidney and hence their exposure is not increased in mild-to-severe renal impairment[14]. In the recently published AWARD-7 study comparing dulaglutide vs insulin glargine in patients with T2DM and moderate-to-severe CKD, both dulaglutide and insulin glargine were equally effective in glycemic reduction. However, the decline in eGFR change was significantly smaller for both dulaglutide doses compared with insulin glargine[30]. Based on this study, dulaglutide has now been recommended for use without dose adjustment in T2DM patients having eGFR upto 15 ml/min/1.73[2]. Liraglutide and semaglutide are the other GLP-1RAs having similar recommendation for use[14].

Thus, given the extensive clinical experience, demonstrated glycemic efficacy with benefits of weight reduction, no hypoglycemia, cardiovascular and renal benefits, GLP-1 RAs can be the preferred noninsulin injectable option especially in T2DM patients with established ASCVD and in T2DM patients who fail to achieve the desired glycemic control with multiple oral AHAs.

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