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Saudi Consensus for GLP-1 RAs Switching Guidance: Consensus Report

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Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) provide adequate glycemic control, weight reduction, low risk of hypoglycemia, and CV risk reduction. Their usage for type 2 DM (T2DM) is recommended mainly when hypoglycemia or weight gain should be considered, also, whenever initial therapy is failed. There are many recent updates in the treatment paradigm of T2DM. There are many types of GLP-1RAs, with a knowledge gap regarding switching between the different types. A Saudi task force gathered to develop an explicit, evidence-based consensus for switching between GLP-1RAs, when, why, and how? This article contains the expert panel's recommendations as a contribution to complement the knowledge gap in this area from the national perspective. As an alternative to intensifying therapy, switching from one GLP-1RA to another has various advantages. Improvements in glycemic control, weight loss, adherence, and medications with established cardiovascular benefits are among them. Also, switching needs to be individualized upon many discussed factors like the dose of the previous GLP1-RA and gastrointestinal adverse effects. Discussion with patients about the why and how to switch is critical.

Keywords

Glucagon-Like Peptide-1 Receptor Agonists, Switching, Type 2 DM, Glycemic Control

1. Introduction

Diabetes mellitus (DM) prevalence is rising quickly not only globally (by the year 2045 it is expected to become 9.9% with a total number of 629 Million), but also in Saudi Arabia (KSA) with its great impacts on both morbidity and mortality [1] [2].

Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) provide effective glycemic control, weight reduction, low risk of hypoglycaemia and CV risk reduction. Both the American Diabetes Association (ADA) guidelines and the ADA/European Association for the Study of Diabetes (EASD) consensus report, recommended their usage for type 2 DM (T2DM), particularly when hypoglycemia or weight gain should be considered. In addition, they recommended their usage whenever a failure of initial therapy with metformin and comprehensive lifestyle modifications [3] [4] [5] [6].

Among the several GLP-1RAs developed, exenatide, liraglutide, semaglutide, and dulaglutide are available in the Saudi market. They have some differences in terms of their kinetics and dynamics [6]-[14]. Exenatide, liraglutide, lixisenatide, oral semaglutide are used on a daily base, either once or twice as in the case of exenatide. However, dulaglutide, exenatide extended-release and semaglutide are used once per week [15] [16].

Of all GLP-1RAs currently available, dulaglutide, liraglutide and once weekly semaglutide have demonstrated CV benefits, based on the results of several trials [9] [11] [12]. Therefore, their usage for patients with established atherosclerotic CV disease was recommended by the ADA. Also, other guidelines recommended their usage for those patients irrespective of glycemic control [3] [5] [17].

There are many recent updates in the treatment paradigm of T2DM in the light of new evidence available. There are many types of GLP-1RAs, with a knowledge gap regarding how to switch between the different types. Switching from one GLP-1RA to another may be beneficial and may delay the need to intensify therapy, thus avoiding an increase in the treatment burden. That may enable the reduction of the dose of concomitant oral anti-hyperglycemic drugs and/or insulin; therefore, improving the adherence to treatment [18].

We, a Saudi task force, gathered to develop an explicit, evidence-based consensus for switching between GLP-1RAs, when, why and how? This article has the recommendations of this expert panel.

2. Insights from Available Literature

The task force searched the medical literature for any manuscript about switch-

ing from one GLP-1RA to another. In addition to the available randomized controlled trials and real-world studies, the task force found two eminent review articles; one review by Almandoz *et al.* provided advice on switching between GLP-1RAs in clinical practice; and also did another recent review was about switching between GLP-1RAs by Jain *et al.* [18] [19].

1) GLP-1RAs have a good impact on glycemic control as well as weight reduction

Glucose-lowering efficacy differs between GLP-1RAs. That has been observed in both clinical trials and analyses of real-world data of GLP-1RA-naïve patients [20]-[27]. The differences in HbA1c and weight reduction in GLP1-RA-naïve patients are shown in **Table 1**.

In addition, switching from one GLP1-RA to another led to improved glycemic control and weight reduction in both randomized controlled trials and retrospective observational studies (**Table 2**) [28]-[35].

These studies, therefore, demonstrate that switching between GLP-1RAs can provide additional benefits in terms of glycemic control and further weight loss.

2) GLP1-RAs have cardioprotective benefits

Some GLP1-RAs have proven cardio protective benefits like OW semaglutide, liraglutide, dulaglutide. Therefore, their indications for use have been expanded in some countries to reduce the risk of major adverse CV events in adults with T2DM and established CVD [9] [11] [12] [36] [37] [38]. On the other hand, others have not proven cardioprotective benefits like lixisenatide and exenatide ER [39] [40].

Why do we need to switch from one GLP1-RA to another?

There are many drives to switch from one GLP1-RA to another. First is the need for further glycemic control and further weight reduction. The second drive to switch is the need for cardioprotection. Other motives to switch are more safety and tolerability, patients' preferences and adherence issues, and more convenient devices [18].

One of the reasons behind the reduced efficacy of GLP1-RAs is the development of increasing antibody titer as seen in an analysis of exenatide clinical trials [41].

The available GLP1-RAs have variable safety profiles. Short-acting GLP1-RAs are more likely to cause nausea and/or vomiting. Long-acting GLP1-RAs are more likely to cause diarrhea [42] [43]. Therefore, switching from one GLP1-RA to another may help alleviate these adverse effects [44].

Poor adherence reduces the effectiveness of therapy. Improved glycemic control was observed for GLP1-RAs in patients with good adherence compared with poor adherence [45] [46] [47]. First, adherence is affected by the frequency of dosing. Several studies demonstrated that as the frequency decreases, the adherence to GLP1-RA is increased [48] [49] [50]. More adherences were observed with OW GLP1-RAs than the daily-based GLP1-RAs [51] [52] [53] [54].

Table 1. HbA1c and weight reduction in GLP1-RA-naïve patients.

DURATION 6 [20]	Reduction	Liraglutide 1.8 mg	Exenatide ER 2.0 mg
	HbA1c	1.5%	1.3%-point
	Weight	3.6 kg	2.7 kg
HARMONY 7 [21]	Reduction	Liraglutide 1.8 mg	Albiglutide 50 mg
	HbA1c	1.0%	0.8%-point
	Weight	2.2 kg	0.6 kg
LIRA–LIXI [22]	Reduction	Liraglutide 1.8 mg	Lixisenatide 20 µg
	HbA1c	1.8%	1.2%-point
	Weight	4.3 kg	3.7 kg
AWARD 6 [23]	Reduction	Liraglutide 1.8 mg	Dulaglutide 1.5 mg
	HbA1c	Same	
	Weight	3.6 kg	2.9 kg
Feher *et al.* [24]	Reduction	Liraglutide 1.8 mg	Lixisenatide 20 µg
	HbA1c	Mean treatment difference [95% confidence interval (CI)] −0.3%-point [−0.56; −0.04])	
SUSTAIN 3 [25]	Reduction	OW semaglutide 1.0 mg	Exenatide ER 2.0 mg
	HbA1c	1.5 %	0.9%
	Weight	5.6 kg	1.9 kg
SUSTAIN 7 [26]	Reduction	OW semaglutide 0.5 mg	Dulaglutide 0.75 mg
	HbA1c	1.5 %	1.1%
	Weight	4.6 kg	2.3 kg
		OW semaglutide 1 mg	Dulaglutide 1.5 mg
	HbA1c	1.8%	1.4%
	Weight	6.5 kg	3 kg
SUSTAIN 10 [27]	Reduction	OW semaglutide 1.0 mg	Liraglutide 1.2 mg
	HbA1c	1.7%	1.0%
	Weight	5.8 kg	1.9 kg

Table 2. HbA1c and weight reduction after switching to another GLP1-RA.

DURATION 1 [28]	From exenatide twice daily 10 µg	To exenatide ER 2.0 mg
	Further decreases in HbA1c levels of 0.2%-point.	
LEAD 6 [29]	From exenatide twice daily 10 µg	To liraglutide 1.8 mg
	Further decreases in HbA1c levels of 0.3%-point and weight decreased by 0.9 kg.	

Continued

CIBELES Project [30]	From another GLP-1RA	To exenatide ER
	Further decreases in HbA1c levels of 0.4%-point with no significant changes in weight.	
Visaria *et al.* [31]	From another GLP-1RA	To OW semaglutide
	Further decreases in HbA1c levels of 1.3%-point.	
REALiSe-DM [32]	From either liraglutide or dulaglutide	To OW semaglutide
	Further decreases in HbA1c levels of 0.7%-point. The mean reduction in weight was 1.6 kg following the switch.	
Watanabe *et al.* [33]	From exenatide twice daily	To exenatide ER
	Further decreases in HbA1c levels of 0.2%-point over 24 weeks. Incidence of hypoglycemia was also significantly reduced. No significant changes in weight.	
Goncalves and Bell study [34]	From liraglutide 1.8 mg	To OW semaglutide average dose 0.76
	HbA1c decreased from 7.46% ± 1.36% to 6.68% ± 1.00% The number of patients requiring insulin dropped from 16 to 13. Weight dropped from 110.6 ± 20 to 106 ± 27 kg.	
Overgaard *et al.* modeling study [35]	From another GLP-1RA	To OW semaglutide
	More reductions in HbA1c Further weigh reduction.	

Moreover, patient preference studies indicated that the injection frequency is highly considered by both injection-naïve and -experienced patients when selecting a GLP1-RA [55] [56] [57] [58] [59].

Therefore, switching from one GLP1-RA that is dosed either once or twice daily to another OW agent may improve adherence and outcomes in some patients. Despite both being OW GLP1-RAs, adherence to dulaglutide was significantly higher than exenatide ER. That indicates factors other than the frequency of dosing are also critical when considering adherence [53].

Technology-related issues are other factors affecting the decision to switch due to convenience. GLP1-RAs devices are variable. The delivery device and needle size are essential when selecting between GLP-1RAs [59]. The needle size varies between GLP1-RAs devices from large diameter (23-gauge in exenatide OW [60], 29 - 31 gauge for exenatide twice daily, and 29-gauge for dulaglutide) and a smaller diameter (32-gauge in OW semaglutide) [9] [61] [62]. A decision to switch, based on the delivery device, should only be made if a patient indicates that they have had difficulty using the injection device of their current GLP1-RA. Also, another factor is the ability to allow micro-titration (*i.e.*, titration to intermediary doses); allowing slower up-titration may help manage GI adverse effects is a significant factor [18] [63]. In addition, the degree to which the dose can be selected varies between GLP1-RA injection devices.

In the summary difference in potency, dosage frequency and adherence, duration of action see table. In general, data suggest that long-acting GLP1-RAs have greater effects on HbA1c, fasting plasma glucose, and body weight than those that are short-acting [13].

3. When to Switch from One GLP1-RA to Another?

There are several medical causes for switching. They are poor glycemic control, more weight reduction is needed, CV risk increased, or the presence of more advanced chronic kidney disease (CKD), and adverse effects. Non-medical causes are patient preference, cost, better technology, and insurance decrees [18] [19]. The following table illustrates these reasons and what to do in each (**Table 3**).

4. How to Switch from One GLP1-RA to Another?

An individualized approach should be considered [18] [19] once the decision has been made to switch from one GLP1-RA to another. Many factors should be considered; one of them is the reimbursement requirements, if any.

Consider any contraindications

Any contraindications or warnings should be considered when switching (**Table 4**).

Selecting the dose to initiate

If the patient has a history of GI adverse effects with his GLP1-RA, switch to one that enables gradual up-titration (**Figure 1**). Initiate it at the lowest dose. For example, 0.25 mg in OW semaglutide and 0.75 mg in dulaglutide. If the patient had no or minimal GI AEs with his GLP1-RA, start OW semaglutide 0.5 mg. Adjust the duration before up-titrating the new GLP-1RA according to the

Table 3. Drivers for switching and what to do in each.

When to switch	What to do
Target HbA1c is not achieved because of:	
• Poor adherence	Switch to an OW GLP-1RA
• Disease progression or lack of efficacy of the current GLP1-RA	Switch to an agent with proven better glycemic efficacy
• The development of anti-drug antibodies	Switch to different types of GLP1-RA Switch to a human GLP-1 analogue
The need for additional weight loss	The most effective GLP1-RA is OW semaglutide. [3]
Increased CV risk in T2DM	[9] [11] [13]
• Established CVD	Dulaglutide, liraglutide or OW semaglutide
• Multiple CV risk factors	Dulaglutide
More advanced CKD status: eGFR < 30 mL/min/1.73 m^2	Switch to a dulaglutide, liraglutide or OW semaglutide [9] [10] [11] [12] [63]
Adverse effects	Switch to another GLP1-RA [44]

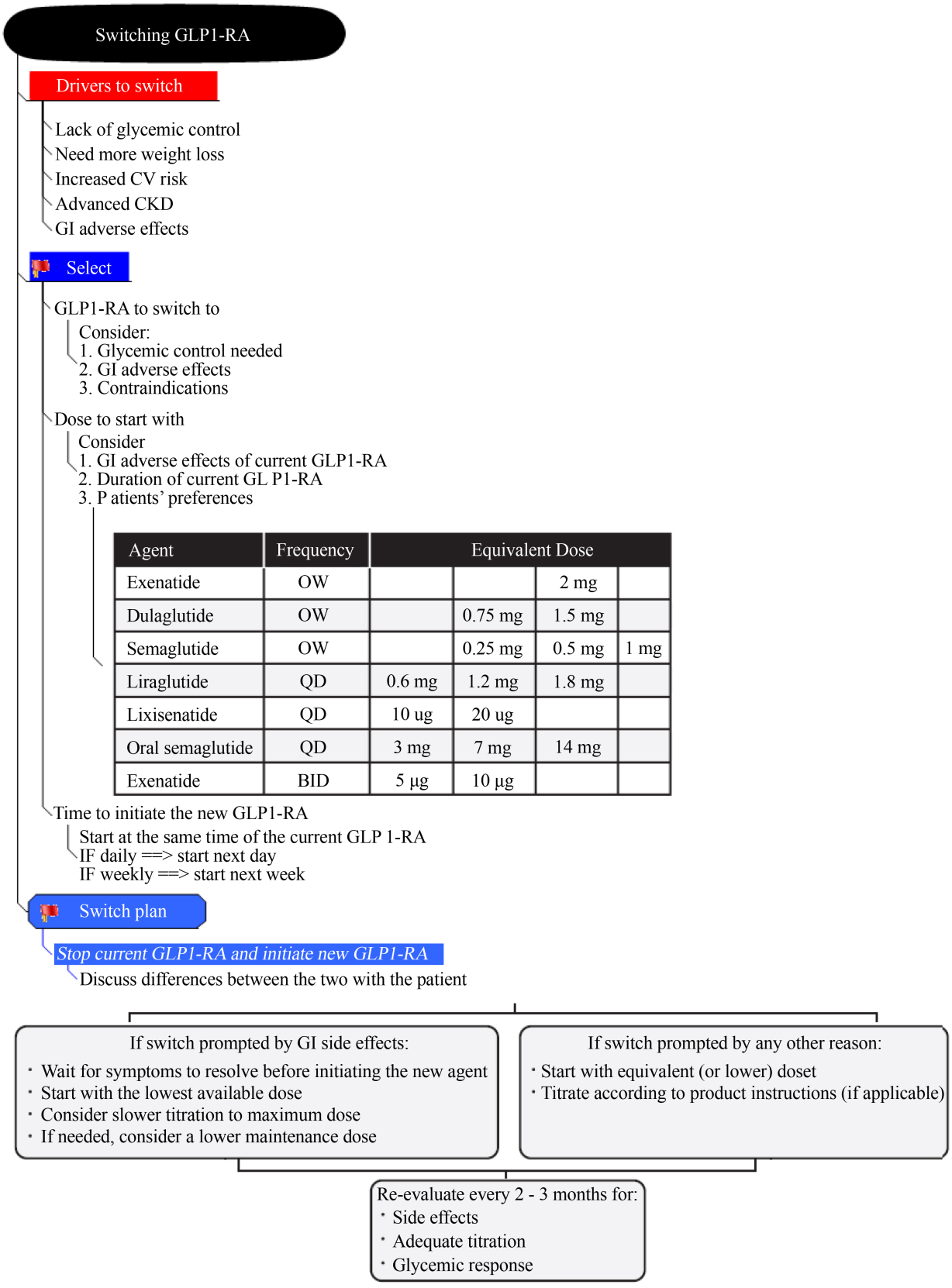

Figure 1. Switching plan to a new GLP-1RA. BID, twice daily; GI, gastrointestinal; GLP1-RA, glucagon-like peptide-1 receptor agonist; OW, once weekly; QD, once daily.

Table 4. Contraindications for switching.

GLP1-RA	Contraindication
Renal impairment	
Majority of the available GLP1-RAs except OW semaglutide, Liraglutide and dulaglutide [6]-[12] [63]	**End-stage renal disease** (estimated glomerular filtration rate [eGFR] < 15 mL/min/1.73 m^2)
Exenatide ER and exenatide twice daily [6] [8]	**Severe renal impairment** (creatinine clearance < 30 mL/min): do not use **Moderate renal impairment** (creatinine clearance 30 - 50 mL/min): use with caution
Lixisenatide [7]	Severe renal impairment
Liraglutide [12]	Renal impairment (eGFR < 60): caution in dose escalation
Dulaglutide [11]	Severe renal impairment
Diabetic retinopathy	
OW semaglutide and dulaglutide [9] [63] [64]	OW semaglutide and dulaglutide are up-titrated more slowly (every 2 - 3 months). Patients should have regular assessments for retinopathy

presence and severity of GI AEs with the previous GLP-1RA. If GI AEs were absent or minor, then up-titrate (every two weeks). If substantial GI AEs are there, then up-titrate more slowly (every four weeks). If a patient was on the current GLP1-RA for less than one month, consider him a GLP-1RA-naïve patient. If he was on it for more than one month, consider the current GLP1-RA dose when calculating the dose of the new one [9] [11] [18] [19].

Timing of the first dose of the new GLP1-RA

The first dose of the new GLP1-RA should be at the time of the next dose of the previous GLP1-RA [18] [19].

Consider concomitant therapy when initiating the new GLP1-RA

The dose of **sulphonylurea or insulin** may need adjustment when switching to reduce the risk of AEs. Sulphonylurea dose should be reduced by 50%, insulin by 20%, and close monitoring for hypoglycemia [18] [65]. Dipeptidyl peptidase-4 inhibitors should be stopped when initiating a GLP1-RA [4].

Deal with barriers to switch:

Patients may feel that they are doing well and do not need to change. In addition, they have concerns about GI AEs. Moreover, the change of devices may be a barrier for some patients. Finally, the increased cost or reimbursement issues may be present. Discuss with the patient about the benefits obtained, and reassure that GI AEs are transient. Also, emphasize that the treatment cost and burden will not be increased [15] [18].

5. Conclusion

In conclusion, switching from one GLP1-RA to another has several benefits as an alternative to intensifying therapy. These include improving glycemic control, more weight reduction, more adherence, and drugs with proven CV benefits. Also, switching needs to be individualized upon many discussed factors like the dose of the previous GLP1-RA and GI AEs. Discussion with patients about the why and how to switch is critical.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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