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Therapeutic approach of type 2 diabetes mellitus with GLP-1 based therapies

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Abstract

The goal of this review is to think about how to incorporate the GLP-1 based agents, represented by the dipeptidyl peptidase-4 (DPP-4) inhibitors or the glucagon-like peptide-1 (GLP-1) analogs, in the guidelines for the management of type 2 diabetes (T2DM). Orally administered DPP-4 inhibitors, such as sitagliptin and vildagliptin, reduce HbA_{1c} (absolute values) by 0.5-1.1% (5 to 12%, relative values), with few adverse events and no weight gain. The sub-cutaneous injected GLP-1 analogs show larger reductions in HbA_{1c} (0.8-1.7%, absolute values; 9.4-20.0%, relative values), associated with weight loss (1.75-3.8 kg); their most common adverse events are gastrointestinal symptoms which contribute to a substantial treatment interruption.

If they do not challenge the use of metformin as the initial therapy of T2DM, several studies argue in favour of the use of DPP-4 inhibitors, either in combination with metformin as the initial treatment or, in add-on therapy to metformin. The advantages of this combination over others currently used are reviewed. In patients not tolerating metformin, DPP-4 inhibitors seem to be an excellent alternative as a monotherapy. As long as oral triple therapy is concerned, the choice for the association metformin + thiazolidinedione + incretin-based drug, has again several theoretical advantages against other triple therapy combinations. Finally, in patients with T2DM inadequately controlled with maximal tolerated oral multi-therapies, GLP-1 agonists are a good alternative to insulin therapy, allowing reaching a better glycaemic control together with a weight loss. However, for patients who do not tolerate GLP-1 agonist treatment, and for those not reaching the HbA_{1c} target, insulin will remain necessary, allowing getting a better metabolic control, with few adverse events. The long-term effect of these new agents on glycaemic control has not yet been established, and their potential impact on β-cell function in humans remains an area of active investigation. So, further studies are needed and will allow progressively refining the use of incretin-based agents in T2DM treatment strategy.

Résumé

Approches thérapeutiques fondées sur les médicaments de l'effet incrétine dans le diabète de type 2

L'objectif de cette revue est d'envisager comment intégrer dans les recommandations actuelles pour la prise en charge et le traitement du diabète de type 2 (DT2), les nouveaux agents fondés sur l'effet incrétine, représentés par les inhibiteurs de la dipeptidyl peptidase-4 (DPP-4) et les analogues du glucagon-like peptide-1 (GLP-1). Les inhibiteurs de la DPP-4, s'administrant par voie orale, telles la sitagliptine et la vildagliptine, réduisent le taux d'hémoglobine glyquée (HbA_{1c}) de 0,5-1,1% en valeur absolue (5 à 12% en valeur relative), avec peu d'effets indésirables et sans prise de poids. Les analogues du GLP-1, s'administrant sous forme d'injections sous-cutanées, entraînent une réduction plus importante du taux d'HbA_{1c} (0,8-1,7% en valeur absolue; 9,4-20,0% en valeur relative), associée à une perte de poids (1,75-3,8 kg) ; leurs effets indésirables les plus fréquents sont des symptômes gastro-intestinaux, responsables d'un taux substantiel d'arrêt du traitement.

Si elles ne remettent pas en cause la place de la metformine en tant que traitement de première intention du DT2, de nombreuses études sont en faveur de l'utilisation des inhibiteurs de la DPP-4, soit en association avec la metformine comme traitement initial, soit en association avec celle-ci dès lors qu'elle ne permet pas, en monothérapie, d'obtenir un contrôle optimal de la glycémie. Les avantages de cette association sur les autres associations en bithérapie actuellement possibles sont discutés. Chez les patients qui ne tolèrent pas la metformine, les inhibiteurs de la DPP-4 en monothérapie paraissent être une excellente alternative à la metformine. Pour ce qui concerne la trithérapie orale, le choix d'une association metformine + thiazolidinedione + médicament de l'effet incrétine, paraît présenter de nombreux avantages

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théoriques par rapport aux triples associations actuellement possibles. Enfin, chez les patients ayant un DT2 dont le contrôle glycémique est insuffisant malgré une multi-thérapie aux doses maximales tolérées, les agonistes du GLP-1 semblent une alternative intéressante à l'instauration d'une insulinothérapie, en permettant d'améliorer le contrôle glycémique et de perdre du poids. Cependant, chez les patients ayant un DT2 ne tolérant pas le traitement par les agonistes du GLP-1 et chez ceux chez qui ils ne permettent pas d'atteindre l'objectif d'HbA_{1c} défini par les recommandations actuelles, l'insuline, titrée de manière optimale, demeurera nécessaire, car permettant d'obtenir un meilleur contrôle glycémique avec peu d'effets indésirables. L'effet de ces nouveaux médicaments sur le contrôle glycémique à long terme demeure encore à être établi, et leur bénéfice potentiel sur la fonctionnalité des cellules β-pancréatiques fait l'objet de très nombreux travaux. Des études additionnelles sont donc nécessaires, et devraient permettre, tout comme les nombreuses études en cours, de mieux définir et d'affiner progressivement la place des médicaments fondés sur l'effet incrétine dans la stratégie thérapeutique du DT2.

Keywords: DPP-4 inhibitors; GLP-1 agonists; Incretin-based agents; Treatment strategy; Type 2 diabetes mellitus

Mots-clés : Agonistes du GLP-1 ; Diabète de type 2 ; Inhibiteurs du DPP-4 ; Médicaments de l'effet incrétine ; Stratégie thérapeutique

1. Introduction

The underlying pathogenic phenomenons in patients with type 2 diabetes (T2DM), and especially impaired insulin secretion, worsen over time, necessitating the use of anti-hyperglycaemic drugs, often in combination, to control glycaemic levels.

Consensus recommendations for the treatment of T2DM have recently been published [1-2]. These guidelines emphasize the long-term maintenance of glycaemic control, as estimated by levels of glycated haemoglobin (HbA_{1c}), as close to the nondiabetic range as is safely possible. They also emphasize the initiation of treatment with metformin in patients who have newly diagnosed disease (concurrent with lifestyle interventions) and the changing of medications no less frequently than every three [1] or six [2] months if HbA_{1c} levels are above the respective targets (Fig. 1).

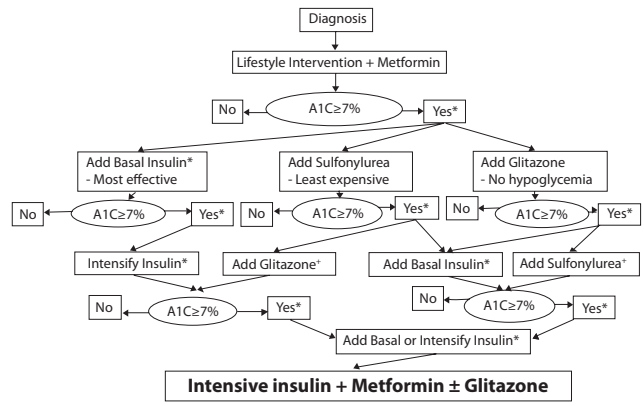

Fig. 1. American Diabetes Association-European Association for the Study of Diabetes (ADA-EASD) guidelines for the metabolic management of type 2 diabetes [Reprinted from Ref. 1].

In combination with metformin and lifestyle interventions, α-glucosidase inhibitors (for the French guidelines), thiazolidinediones (TZD), and sulfonylureas (SU) are included as possible next-step oral medications if metabolic goals are not achieved or maintained. Besides the possibility to use triple oral therapy (metformine + TZD + SU), the algorithms includes also earlier, aggressive use of insulin, the most powerful antidiabetic drug.

However, the increasing number of available medications (some have been recently approved and others will be in the near future) makes these recent guidelines already obsolete and will need to update them in order to help clinicians for a rational integration of these new anti-diabetic medications in the current recommendations.

The goal of this paper is to think about how to incorporate the new class of antidiabetic agents, represented by the dipeptidyl peptidase-4 (DPP-4) inhibitors or the glucagon-like peptide-1 (GLP-1) analogs, in the current guidelines, according to already published works and what we know about the mechanisms of action, and the safety and tolerability of these drugs.

A recent meta-analysis [3] has reported the results, in term of efficacy and tolerability, of the clinical studies involving incretin-based drugs. As in the meta-analysis, we have considered only clinical studies involving T2DM patients. However, several differences exist between this meta-analysis and this present review:

- only clinical studies that lasted at least 12 weeks are considered in this review;
- only the results obtained with the usual daily doses of the respective incretin-based agents are taken into account: 100 mg qd (or 50 mg bid when 100 mg was not used) for the DPP-4 inhibitors, vildagliptin and sitagliptin (except for the association of vildagliptin with SU where 50 mg qd will be the recommended dose) and, for the GLP-1 agonists, at least 1.8 mg for liraglutide, 5 µg bid for 4 weeks, then 10 µg bid, for exenatide, and 2 mg for exenatide administration of a long-acting release (LAR) formulation;
- some studies selected in this review were not included in the meta-analysis [4-10];
- instead of being presented according to the molecule, the results are expressed according to the type of the study, within the DPP-4 inhibitor studies from one hand, and the GLP-1 agonists from the other hand: mono or combination therapy, versus placebo, or versus active drugs;