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EDITORIAL

Safety and benefit of incretin-based therapies in patients with type 2 diabetes: learnings and reflections

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1. Introduction

Over the past two decades, the treatment landscape for type 2 diabetes (T2DM) has witnessed a remarkable increase in the number of drug classes available for the management of hyperglycemia; in addition to the traditional medications, several newer agents have found their place in the multi-targeted approach to controlling this global health challenge, even bringing diabetes to remission [1]. Among novel antidiabetic agents are the incretin-based therapies (IBTs), working on the gastrointestinal-hepatopancreatic-brain axis through the modulation of gut-derived hormones that play a vital role in maintaining euglycemia and regulating appetite [2]. Two major classes of IBTs are at hand to accomplish this goal; the glucagon-like peptide-1 receptor agonists (GLP-1RA) largely mimic the actions of GLP-1 and can best be viewed as supplementary therapies [3]. On the other hand, the dipeptidyl peptidase-4 inhibitors (DPP-4i) serve to prolong the half-life of native GLP-1 and enhance its inherent favorable actions; thus, their action is dependent on the presence of an intrinsic reserve of gut-derived hormones [4].

2. Safety and benefit of incretin-based therapies

Regardless of the class and type of therapies, a critical aspect of their general acceptance and durability of use remains the demonstration of reasonable side-effect and tolerance profiles in human subjects, together with demonstration of significant clinical benefit [3,4]. This is particularly relevant in a historical context, as there are examples of efficacious medications such as the thiazolidinediones that faced withdrawal from the market in light of undesirable post-marketing experience for an adverse cardiovascular profile [5], most likely for unfavorable increase of atherogenic lipoproteins [6]. Indeed, T2DM patients usually have increased triglyceride levels together with reduced concentrations of high-density lipoproteins (HDL) and a predominance of small, dense low-density lipoproteins (LDL) particles [7,8]. Together these factors substantially contribute to the cardiovascular risk of such patients, since these atherogenic subspecies are closely associated with endothelial dysfunction and inflammatory response in the vascular wall [9,10]. The rosiglitazone lesson led clinicians to consider drug safety as a priority, and it is incumbent upon us to never let our guard down in the use of any novel antidiabetic medication; this is especially pertinent during the current coronavirus disease COVID-19 pandemic, since diabetic patients are among those exposed to the most serious forms of the disease and related mortality [11].

Concurrently, it is becoming increasingly evident that ethnicity can have a major impact on drug pharmacokinetics, metabolism, side-effect profile, and clinical benefit. Several underlying mechanisms may be responsible for ethnicity-based variability in drug response, and these vary from differences in metabolic rates to receptor sensitivity and molecular processes [12,13]. Indeed, these variations, if predictably mapped out, could form the basis of the emerging knowledge of personalized medicine. First and foremost, however, clinical and notable safety and tolerability data has to be gathered in a sufficiently robust manner to justify any benefits that may accrue from the use of a particular medication. Of note, the continent of Asia is in the forefront of the rapid increase in the incidence of T2DM [14], and Asian patients stand to benefit greatly from the availability of, and access to, newer medications to combat this rise.

It is from the point of view of the foremost importance of patient safety of IBTs and its reproducibility in individuals of various ethnic backgrounds that the analysis of Kanasakia et al. [15] has significance. The authors have conducted a post-hoc, pooled analysis of 21 randomized, double-blind, placebo-controlled clinical trials of ≤52-week duration with the use of linagliptin, a DPP-4i agent, in participants with T2DM living in East and South Asia. Notably, they evaluated both adverse events (AEs) and laboratory parameters. In addition to the usual AEs that are commonly encountered and documented, certain drug class-specific events such as hypoglycemia, worsening of renal function, pancreatitis, and bullous pemphigoid were also evaluated. The investigators acknowledge the

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shortcomings of their analysis, the predominant being the short duration of some trials that were ostensibly performed to ascertain glycemic efficacy rather than safety. Nevertheless, the pooled data gives credence to the findings and reassuringly concludes that linagliptin appears to be largely safe and well-tolerated in patients of Asian descent, which extends the generalizability of this agent, and perhaps the DPP-4i class as a whole, to beyond populations traditionally studied and where data already exists (such as in Caucasians).

The results of the analysis by Kanasakia and colleagues follow on the heels of other recent publications, attesting favorably to the use of DPP-4i in Asian subjects, two of which involve linagliptin [16–18]. Tomohiro and others [16] have reported the long-term safety and efficacy results of this medication when used as an add-on therapy; over a three-year period, its profile and efficacy were predictably similar to the previously published data. Along similar lines, Watada et al. [17] performed a pooled analysis of five controlled and randomized trials where linagliptin and empagliflozin were used in combination. The safety profile of the fixed-dose combination was similar to the individual monotherapies, and no additional safety signals were identified. Lastly, vildagliptin was found to be well-tolerated in a post-marketing surveillance in Japanese subjects in a real-world setting [18].

3. Expert opinion

There is, therefore, growing evidence that the DPP-4i class is predictable in its clinical safety through a spectrum of ethnic diversity [19]. It also helps to establish IBTs as a reliable class of medications that can move from a novel, esoteric pharmacologic intervention to a more mainstream step in the management of T2DM. In this context, linagliptin not only shares the advantages of the DPP-4i class, namely oral route of administration and minimal gastrointestinal side-effects, but is the only agent in this group that does not require dose adjustment in patients with severe chronic kidney disease. By highlighting the results of their meta-analysis, Kanasakia et al. [15] have contributed to extending the benefits of this medication to Asian patients as well.

The DPPi class has also consistently shown safety for the cardiovascular profile, while benefit has been found with the use of GLP-1RAs and sodium glucose cotransporter 2-inhibitors (SGLT-2i) [20]. The cardiometabolic role of these last two classes of novel antidiabetic agents has been emphasized by the most recent international scientific guidelines issued by both cardiologists and diabetologists, which have clearly suggested that T2DM patients would benefit from an earlier use of antidiabetic drugs with proven cardiovascular benefit, that are GLP1-RAs and SGLT-2i [21]. Yet, the use of these agents is still sub-optimal in T2DM patients, who are exposed to a significant risk of atherosclerotic form of cardiovascular disease [22], and evidence suggests that some GLP1-RAs are even able to reduce atherosclerotic plaque formation and progression, thus with a direct beneficial action on the pathophysiological mechanisms of cardiovascular disease [23].

In conclusion, preventive examinations should be undertaken earlier [24], since coronary atherosclerosis progresses faster in T2DM patients [25], and a comprehensive approach on both glucose and lipid alterations should be considered with proper duration of treatments [26], giving the chance to high-risk patients to reduce the number of major cardiovascular events [27]. Currently, IBTs have a major role in managing T2DM. The DPP-4i agents have consistently shown safety and tolerability, even in patients with different ethnicities, with the convenient oral formulation and favorable compliance to treatment. However, for subjects at high risk or with established atherosclerotic cardiovascular disease, which constitute the majority of T2DM patients managed by specialists, GLP-1RAs have to be preferred for their significant cardiometabolic benefit, even independently of baseline glycated hemoglobin levels [28].

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Declaration of interests

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Reviewer disclosures

A reviewer on this manuscript reports that they have worked with the industry on GLP-1-based therapies for more than 25 years, with consultations and advisory board functions for almost all companies. Currently they serve on several advisory boards for NovoNordisk. All other peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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