Ten Years of Vildagliptin

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After many years of limited therapeutic opportunities, the treatment of type 2 diabetes has become more target and pathophysiologically driven. A typical example is represented by the development of the dipeptidyl peptidase-4 (DPP-4) inhibitors, allowing for more physiological regulation of the endocrine pancreas and leading to a previously unmet risk-to-benefit balance. Vildagliptin, one of the earliest DPP-4 inhibitors, has been tested across the entire spectrum of type 2 diabetes and has been in clinical use for 20 years. This publication critically reviews the main steps in the clinical development of this agent.

Keywords

Type 2 diabetes, DPP-4 inhibitors, vildagliptin

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Until the turn of the century, treatment of hyperglycaemia in type 2 diabetes was limited to two main classes of drugs: sulphonylureas and biguanides. Though belonging to two distinct classes, these drugs shared two main characteristics: the first one is that they have been used to lower blood glucose much longer, before their mode of action could be understood; the second is that they both were the result of serendipitous discovery. In more recent years, through improved understanding of the pathophysiology of the disease, better drugs have been developed to target the specific mechanisms that are responsible for hyperglycaemia, thus providing a more physiological approach to the treatment of type 2 diabetes. A typical example has been the development of inhibitors of the dipeptidyl peptidase-4 (DPP-4) enzyme. This enzyme is responsible for the degradation of many peptides, including incretins, hormones released by endocrine cells in the intestine in response to the ingestion of a meal. Specific DPP-4 inhibitors have been developed because of the appreciation of the critical role played by the incretins, and in particular, glucagon-like peptide-1 (GLP-1), in the regulation of glucose-dependent stimulation of insulin and glucagon secretion, and the potential reduced production of GLP-1 from intestinal L-cells in hyperglycaemic individuals. Under these circumstances, DPP-4 inhibition ensures persistence of endogenously secreted GLP-1 in the systemic circulation. A vast body of literature and many clinical trials have set the basis for the current clinical use of these drugs. These studies have lent the evidence of their efficacy and good tolerability profile. Because of this evidence, DPP-4 inhibitors have become the standard of care and more often used as second-line treatment upon metformin failure or as initial therapy in people with metformin intolerance. Among the DPP-4 inhibitors, vildagliptin is an orally available, small-molecule, competitive reversible DPP-4 inhibitor for the treatment of type 2 diabetes. It is currently used in more than 132 countries around the world, and it celebrates its 20th year in the diabetes pharmacopeia. Over the last two decades, the flexibility and efficacy of vildagliptin, and other DPP-4 inhibitors, have been tested in many clinical conditions with particular references to patients at higher risk, including the elderly, those with impaired kidney function, and those on insulin treatment. With respect to this, the development programme of vildagliptin and its assessment in the clinical setting remains unique among DPP-4 inhibitors, particularly with respect to the two extremes of the curve of the natural history of diabetes, that is, the time of the diagnosis of diabetes and the most advanced stages

as it can occur in elderly people. VERIFY (NCT01528254) is a unique trial designed to determine durability, over a pre-specified 5-year follow-up, of early use of vildagliptin in combination with metformin in individuals at diagnosis or very short duration of disease and mild elevation of glycated haemoglobin (HbA1c). The results of the study will set the reference bar for any future clinical trial exploring early intensive treatment. INTERVAL (Individualised treatment targets for elderly patients with type 2 diabetes using vildagliptin add-on or lone therapy) is the only study so far exploring the potential of DPP-4 inhibitors for target setting in elderly patients. These and all the other clinical studies are discussed in the following articles, providing the reader with all the elements for critical appreciation of vildagliptin as a valuable therapeutic option across the whole spectrum of the disease, i.e., from those with newly diagnosed diabetes to those progressively aging, as well as those living longer with their disease than they ever lived without diabetes. ❑