REVIEW

Emerging options for the treatment of type 2 diabetes in Chinese patients: focus on arterial function and alogliptin

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Abstract: Type 2 diabetes mellitus (T2DM) has become a worldwide health problem, and the rate of it is growing greatly in the People's Republic of China every year. T2DM could cause macrovascular and microvascular complications that lead to an increase in arterial wall thickness, endothelial dysfunction, calcification, and – finally – to an increase in arterial stiffness and arterial dysfunction. Alogliptin, a new selective inhibitor of dipeptidyl peptidase 4, has shown its great antihyperglycemia effect in T2DM patients. The clinical trial data from the People's Republic of China was similar to other global and Asian trials. This could provide some choice for clinical physicians to the treatment of T2DM.

Keywords: type 2 diabetes mellitus, People's Republic of China, alogliptin, arterial function

Introduction

The Report on Cardiovascular Disease in China (2011) showed that there are 230 million patients who suffered from cardiovascular diseases, and the number is growing rapidly.[1] The mortality of cardiovascular disease was significantly higher in the People's Republic of China than in other developed countries.

Type 2 diabetes mellitus (T2DM) is a major risk factor for cardiovascular diseases, and the risk of cardiovascular disease is two to four times as high in people with T2DM as in people without T2DM.[2] In addition, T2DM is a chronic and progressive disease, presenting a major challenge to health care worldwide. The pathogenesis of T2DM is accompanied with a plasma glucose increase and insulin resistance, and it is associated with both microvascular and macrovascular complications, including atherosclerosis and arteriosclerosis, that result in the damage of the kidney, heart, nervous system, and so on. Previous studies have shown that antihyperglycemic treatment could significantly reduce the incidence of cardiovascular-related diseases;[3] however, current drugs could not thoroughly reduce the incidence of cardiovascular diseases with unsatisfied blood glucose control. Exploring the new antihyperglycemic drugs to reduce the complications and death caused by T2DM is always the main goal of global T2DM control strategy.

Alogliptin, a new selective inhibitor of dipeptidyl peptidase 4, has been approved for the treatment of T2DM by the US Food and Drug Administration. Some studies have shown the safety and effective role of alogliptin in T2DM treatment. However, there are few clinical trials in the People's Republic of China at present. The purpose of this paper was to review the current status of T2DM in the People's Republic of China and to introduce the new antihyperglycemic drug alogliptin to the People's Republic

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of China to provide some choice for clinical physicians in the treatment of T2DM.

T2DM in the People's Republic of China

A national study conducted by Yang et al[4] from June 2007–May 2008 to estimate the prevalence of diabetes among Chinese adults showed that there were 92.4 million adults with diabetes (50.2 million men and 42.2 million women) and 148.2 million adults with prediabetes (76.1 million men and 72.1 million women). The prevalence of total diabetes and prediabetes was 9.7% (10.6% among men and 8.8% among women) and 15.5% (16.1% among men and 14.9% among women), respectively.

However, the recent study surveyed by Xu et al[5] in 2010 showed that the prevalence of diabetes was estimated to be 11.6% in Chinese adults, 12.1% in men, and 11.0% in women, with great increasing amplitude when compared to the previous survey. Moreover, only little more than one-third of patients (39.7%) treated for diabetes had adequate glycemic control. These large national surveys document that diabetes has become a major public health problem in the general population of the People's Republic of China. Cardiovascular diseases, stroke, and T2DM will result in US $550 billion in economic losses to the People's Republic of China from 2005–2015 if the measurement of vascular-related diseases, stroke, and T2DM is not improved.

In addition, the 2007–2008 China National Diabetes and Metabolic Disorders Study showed that the prevalence of being overweight/obese or having hypertension, dyslipidemia, or hyperglycemia was 36.67%, 30.09%, 67.43%, and 26.69% in males; and 29.77%, 24.79%, 63.98%, and 23.62% in females, respectively. In the total sample of 46,239 patients, the prevalence of one subject having one, two, three, or ≥ four of the five defined risk factors (ie, smoking, overweight/obese, hypertension, dyslipidemia, or hyperglycemia) was 31.17%, 27.38%, 17.76%, and 10.19%, respectively. Following an adjustment for sex and age, the odds ratio of cardiovascular diseases for those who had one, two, three, or ≥ four risk factors was 2.36, 4.24, 4.88, and 7.22, respectively, when compared to patients with no risk factors.[6] T2DM has become a major public health problem in the People's Republic of China, and antihyperglycemic therapy has become a daunting task in the People's Republic of China to reduce the increasing incidences of cardiovascular diseases.

Arterial function evaluation and T2DM

As we know, T2DM could cause macrovascular and microvascular complications, such as aortic atherosclerosis and retinal artery arteriosclerosis, leading to an increase in the arterial wall thickness, endothelial dysfunction, and calcification, and finally leading to an increase in arterial stiffness.[7] Arterial stiffness is a strong predictor of future cardiovascular events and all-cause mortality. It is one of the earliest detectable manifestations of adverse structural and functional changes within the vessel wall.[8] Arterial stiffness can be measured by pulse wave velocity (PWV) and cardio–ankle vascular index (CAVI).

Our previous studies also showed that the PWV was positively correlated with pulse pressure, and it was increased in hypertension patients with left ventricular hypertrophy.[9,10] Our team also showed that CAVI was significantly higher in the T2DM groups than in healthy persons and positively correlated with glucose.[11] In addition, our previous studies showed the relationship between CAVI, PWV, and plasma lipids, and homocysteine in vascular-related diseases.[12] Mineoka et al[13] found that CAVI was correlated with coronary calcification, indicating that CAVI could be an evaluation index for the macrovascular complication of DM.

As previously mentioned, T2DM is a major risk factor for cardiovascular diseases, and vascular lesion is the basic pathological change. So, in addition to glucose control, arterial function should be considered during the treatment of T2DM, because arterial function evaluation is more important for the prevention of cardiovascular diseases. If we found the vascular function abnormality early, we could treat it early, before cardiovascular diseases attack. This is very important for T2DM patients to reduce the incidence of myocardial infarction or other serious cardiovascular diseases. So, the early detection and treatment of high-risk patients has been enforced as a key strategy in the prevention of cardiovascular diseases, to reduce the incidences of death and disability of cardiovascular diseases – in addition to the treatment of serious vascular events. Vascular medicine is a new discipline, based on the human vascular tree as a whole, and involves the vascular-related diseases, involving the heart, brain, kidneys, lungs, intestines, and other organs. It also includes early detection, prevention, and rehabilitation.

Early vascular lesion detection technology was approved by the Ministry of Health of the People's Republic of China to be promoted to the whole People's Republic of China in 2004. We established the early vascular lesion

detection system and published the first guidelines in 2005[14] – Chinese Guideline for Early Vascular Disease Detection (first report). This guideline was renewed in 2011 as the Chinese Guideline for Early Vascular Disease Detection (2011 second report).[15]

Noninvasive detection technology, such as ultrasound, PWV, CAVI, ankle–brachial index, endothelial function, and biomarkers, has become the main method of an early vascular lesion evaluation system. So – in addition to glucose and hemoglobin A_{1c} (HbA_{1c}) control – arterial function evaluation should be considered during T2DM treatment.

Alogliptin

Alogliptin, a new selective inhibitor of dipeptidyl peptidase 4, has shown its efficacy in T2DM treatment. In a randomized, double-blind, placebo-controlled trial, Seino et al found that alogliptin once daily was safe and effective when added to metformin in Japanese patients with inadequately controlled T2DM on metformin alone, with greater reduction changes from baseline in HbA_{1c}.[16] Seino et al also showed that alogliptin was well-tolerated and dose dependently improved glycemic parameters in T2DM patients who were inadequately controlled on diet and exercise.[17] In addition, the Efficacy and Safety of Alogliptin Plus Metformin Compared to Glipizide Plus Metformin in Patients With Type 2 Diabetes Mellitus (ENDURE) study showed that the efficacy of alogliptin was sustained for 2 years in T2DM patients, with notably fewer hypoglycemic episodes and no negative impact on weight compared with glipizide.[18] T2DM is associated with a higher risk of cardiovascular events, and some glucose-lowering agents may be associated with an increased – rather than a decreased – risk of cardiovascular events.[19,20]

However, the results from Cardiovascular Outcomes Study of Alogliptin in Patients With Type 2 Diabetes and Acute Coronary Syndrome (EXAMINE) study showed that the rates of the major adverse cardiovascular events were not increased with alogliptin as compared with placebo in T2DM patients with a recent coronary syndrome, with lower glycated hemoglobin levels compared with placebo. The incidences of hypoglycemia, cancer, pancreatitis, and initiation of dialysis were similar with alogliptin and placebo.[21] Alogliptin might attenuate atherosclerosis through suppressing the proliferation of vascular smooth muscles and monocyte inflammatory reaction in male apolipoprotein E-deficient mice.[22] So, alogliptin might be a novel molecule for improving glycemic control in T2DM patients.[23,24]

In addition, alogliptin was approved for the treatment of T2DM alone or added on to metformin by the People's Republic of China Food and Drug Administration (CFDA) in 2013. However, there were few clinical trials in the People's Republic of China, and there was only one baseline research study searched. It is a Phase III study[25] to evaluate the efficacy and safety of alogliptin versus placebo in T2DM patients. This was a multicenter, randomized, double-blind, placebo-controlled, 16-week study comparing alogliptin (25 mg, 1 per day) versus placebo as monotherapy, an add-on to metformin, or an add-on to pioglitazone ± metformin. A total of 491 patients were enrolled in the mainland China subgroup of the study. The demographic data, medical history, glycemic profile, and treatment regimen at the baseline are well-balanced. The primary efficacy endpoint was the change in HbA_{1c} from baseline (week 0) to the end of treatment (week 16). The results released by the CFDA showed that the alogliptin monotherapy, alogliptin + metformin, and alogliptin + pioglitazone all produced a significant reduction in changes from baseline in HbA_{1c} (1.00%, 0.91%, 0.75%, respectively; all $P < 0.05$) after 16 weeks.

Further analysis showed that the effect of alogliptin on HbA_{1c} started from week 4 and continued to week 16. In addition, the compliance rate of HbA_{1c} and the fasting blood glucose were preceded to placebo. There were no significant changes about weight between these groups.

Furthermore, the mostly adverse event in the alogliptin group was nutritional and metabolic disorders (10.7%); the incidence of hypoglycemia was 1.6% in the alogliptin group and 0.8% in placebo, similar to other global and Asian trials. There were no other questions about safety except for the content instructions. The result of this study will provide the clinical evidence for the use of alogliptin in Chinese T2DM patients.

In conclusion, T2DM is a worldwide health problem, and the prevalence of T2DM in the People's Republic of China is increasing every year. Alogliptin is a new antihyperglycemic therapy drug showing great prospects, and we should include the arterial stiffness index into the effect evaluation system of alogliptin on T2DM treatment.

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Disclosure

The authors report no conflicts of interest in this work.

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