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Medical use of finererone in patients with diabetes mellitus and chronic kidney disease

Abstract

Chronic hyperglycemia is one of the factors that contributes significantly to the complications associated with diabetes mellitus. Excess glucose causes an imbalance in cellular oxidation/reduction reactions, as well as systemic inflammation and inflammation in the renal parenchyma, playing a critical role in the pathogenesis of diabetic kidney disease, which today is the main reason for dialysis (hemodialysis/peritoneal) in the world. The pathogenesis of the disease is a difficult process to understand and is integrated with other organic and systematic factors; despite the different mechanisms involved in diabetes mellitus-related kidney damage, the biochemical and cellular mechanisms involving the oxidative and inflammatory pathways are widely recognized by science. There is evidence that the persistent state of hyperglycemia triggers oxidative stress and inflammation mediated by deregulated metabolic pathways, in a cycle that repeats itself, promoting the progression of cell damage and kidney disease.

Chronic kidney disease (CKD) is an extremely serious condition that is often underdiagnosed. It is one of the most frequent and serious complications of diabetes. More than 40% of patients with type 2 diabetes mellitus develop CKD. Despite the existence of therapies recommended by the guidelines, patients with CKD and type 2 diabetes have a high risk of CKD progression and cardiovascular events with unfavorable outcomes. It is estimated that CKD affects more than 160 million people with diabetes worldwide. Chronic kidney disease resulting from type 2 diabetes is one of the main causes of advanced kidney disease, requiring dialysis or kidney transplantation. For these reasons, science has set itself the goal of conducting serious and impactful studies into the evolution of kidney disease, in which the key points are the use of drugs aimed at reducing the severity and the rapid natural history of the disease, which as a rule evolves into outcomes that are not always favorable to the patient. Many scientific studies have advanced in this century with an important impact on medicine, such as the FIGARO-DKD and FIDELIO-DKD studies, which seriously analyzes the impact and relevance of the use of mineralcorticoid receptor antagonists, specifically finerenone, in patients with type 2 diabetes mellitus and chronic kidney disease.

Keywords: diabetes mellitus; chronic kidney disease; kidney, diseases; oxidation-reduction; inflammation; oxidative stress; finererone

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Introduction

Persistent hyperglycemia and peripheral insulin resistance are important factors that lead to serious damage and future dysfunction of vital organs, such as coronary heart disease, retinal disease, neurological change and kidney dysfunction itself. Contemporary lifestyles, sedentary lifestyles and an extremely inflammatory diet have not even prevented children from developing type 2 diabetes at an early age.[1] In countries considered to be the first world, women are more affected by diabetes than men, due to their lifestyle and hormonal and environmental factors. The uptake of glucose that results from the action of insulin in the tissues is facilitated by GLUT4 (glucose transporter),[4] which is found mainly in fatty tissues and striated muscles, such as skeletal and cardiac muscles.[3] Innate and adaptive immunity suffer alterations in their control systems and mechanisms, which lead to functional and qualitative deficits during the course of diabetes. Mitochondria are the main cyto organelle in cell metabolism and play an important role in maintaining oxidative balance.[3,4] Diseases related to oxidative stress result in structural and metabolic deficiencies that activate the mitochondrial apoptosis pathway, which in turn results in cell death and decreased ATP production. All these alterations together lead to damage to the kidneys. Diseases related to oxidative stress and deregulations in these important reactions to the functioning of the human body result in structural and metabolic deficiencies that activate the cell apoptosis pathway, which in turn results in cell death and drastic decrease in energy production by the cell. All these changes, together and evolutively, lead to chronic kidney lesions.[2,10]

The FIDELIO-DKD and FIGARO-DKD studies performed in patients with type 2 diabetes and chronic kidney disease reported and observed cardiovascular and renal outcomes at different stages of chronic kidney disease. The objective of the FIDELITY analysis was to examine an efficacy and safety study at a pre-specified individual level in a broad spectrum of CKD to more robustly estimate the safety and effectiveness of finerenone compared to the placebo group.[5] Finerenone presents itself as a medically acting non-steroidal and selective Mineralocorticoid receptor (MR) antagonist, which has been shown to be an alternative to other medications that have many adverse effects. The overactivation of the mineralcorticoid activating system is an important factor for the evolution of the disease, since such overactivation is one of the main causes of renal and cardiac damage. Chronic and persistent stimulation of the mineralocorticoid receptor (MR) corroborates fatally for inflammation and fibrosis in the kidneys and heart.[5,9] The drug Finerenone is interesting as it did not show any relevant affinity to the receptors of androgens, progestogens and estrogen, receptors and therefore does not cause side effects linked to deregulations in these hormones. Its MRI binding leads to

a specific receptor binding complex that blocks the re-establishment of transcriptional coactivators involved in the expression of pro-inflammatory and pro-fibrotic mediators, moreover, as previously dictated, the drug Firinone has potential advantages over the use of other medicines of the same class due to its high degree of selectivity and low degree of unfavorable side effects.[5,11] The risk of severe elevation of potassium in the blood was lower with the use of finerenone than with the use of spironolactone,[9] which is, finerenone has caused relatively low rates of severe serum elevations of potassium ion, leading to lower percentages and drug discontinuation events ranging from almost 2 to 3.2%. It also presented with an effect on hemodynamics very little expressive, that is, in addition to all the benefits mentioned earlier, it does not severely interact with the functional homestase of the perfusion system, ventilation and cardiac debit. In addition, there were lower falls in the glomerular filtration rate with finerenone than when compared to the use of spironolactone.[5]

The FIDELIO-DKD study was an important, scientifically randomized, in which the effect of the use of Finerenone in patients with chronic kidney disease and type 2 diabetes mellitus was described and studied when compared to the placebo group. Patients were randomly selected based on albuminuria level (> 30 mg/g), glomerular filtration rate of 25 to 75 mL/min/1.73m2 and blood potassium level (4.8 mmol/L), and should have received standard treatmentgold, including a tolerated dose of angiotensin converting enzyme inhibitor or angiotensin receptor blocker. One of the most important outcomes that the study brought was to compose the results through categories, such as categorizing the patient for the time until the first occurrence of renal failure (defined as renal replacement therapy or a sustained decrease in glomerular filtration rate to < 15 mL/min/1,73m2 in at least 4 weeks or a sustained decline in glomerular filtration rate of 40% or more compared to baseline at least 4 weeks or renal death). Another secondary outcome was a compound of time until the first occurrence of cardiovascular death (CV), non-fatal heart attack, non-fatal stroke or hospitalization for heart failure.[5,8]

The study surveyed and examined more than 5,000 patients randomly selected to receive finerenone once aday or receive placebo, with an average follow-up duration of more than 2.5 years. After patients were informed about the end of the study, the vital state was analyzed and success was achieved in more than 99% of patients. Finerenone showed superiority over the placebo group, significantly reducing the risk of the preliminary composite result compared to placebo in a time-to-event analysis using the scientific biostatistic model. Finerenone also significantly decreased the risk of major secondary composite outcome from time to first occurrence of CV death, non-fatal heart attack, non-fatal stroke or hospitalization for heart failure compared to placebo. For the secondary outcome of change in the median albumin/creatinine ratio of urine from beginning to month 4, a relative reduction of more than 30% was observed in the finerenone group compared to the other placebo group.[5,8]

In another study carried out in addition to the FIDELIO-DKD study, the FIGARO-DKD study in which he examined patients with type 2 diabetes who had more advanced chronic kidney disease and with moderately high albuminuria or early stages of chronic kidney disease with severe albuminuria, was shown that supervised therapy with the finerenone medication improved cardiovascular parameters when compared with placebo. Patients who received the medication had a lower risk of death due to cardiovascular causes, non-fatal heart attack, non-fatal stroke or hospitalization due to heart failure than those in the placebo group.[8] This difference was also analyzed by the outcome that there was a lower incidence rate of hospitalization for heart failure in the group that used finerenone.[7] In trials, the noted cardiovascular benefits of finerenone therapy were clinically substantial and were achieved on a background of guideline directed therapy, including renin-angiotensin-system blockade at a highest dose that did not cause several side effects, as well as frequent use of cardiovascular medications as statins and controlled glycated hemoglobin (HbA1c) and blood pressure levels. In the trial, the cardiovascular benefits of finerenone therapy were consistent across categories according to the baseline urinary albumin-to-creatinine ratio and glomerular filtration rate.

In these studies, the remarkable cardiovascular benefits of finerenone therapy were clinically substantial and important, in addition to being guided through a therapy fund based on the therapeutic guidelines of medical societies, as seen in the use of drugs that induce renin-angiotensin-system blockade at a higher dose that does not cause various side effects, as well as frequent use of cardiovascular drugs such as statins and controlled glycated hemoglobin (HbA1c) and blood pressure levels. In the trial, the cardiovascular benefits of finerenone therapy were consistent across categories according to the baseline urinary albumin-to-creatinine ratio and glomerular filtration rate. More than 60% of patients had chronic kidney disease with albuminuria and glomerular filtration rate of at least 60 mL/min/1.73m2 at baseline, which highlights the need for early diagnosis of chronic kidney disease with laboratory urinary and serum dosages of albumin and creatinine for, thus, we continue with treatment to improve results in this poorly recognized population of patients with a high or very high cardiovascular risk.[5,8]

Overview

Although the studies and the use of Finererone are promising and tend to be part of the strategic treatment of kidney disease in diabetes, it is important to emphasize that a low-carbohydrate diet, glycemic control, weekly physical activity and a total change in lifestyle, in addition to the control of systemic arterial hypertension andits complications, is still the therapeutic pillar for the deterioration of target organs, especially the kidneys. Therefore, finerone should be considered under the right conditions, but always in addition to individual therapeutic treatment, as it does not replace the main non-pharmacological measures in the therapeutic regimen.ineralcorticoid receptor antagonists have been used in medical practice to manage systemic arterial hypertension and chronic kidney disease for many years, but research has not produced sufficient evidence of clinical benefit for people with diabetes-related nephropathy.[8] Currently, the use of an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker is recommended for people with diabetes, hypertension and albuminuria, and can also be considered in people with diabetes and albuminuria, but with normal blood pressure levels, i.e. without hypertension.[9] Recent evidence shows that finerenone could be a promising therapy for these patients and that soon, with the success of retrospective and current studies, it could be the basis of therapy.

Conclusion

In the FIGARO-DKD study, which observed patients with type 2 diabetes who had more advanced chronic kidney disease and moderately high albuminuria or early stages of chronic kidney disease with severe albuminuria and who received finererone, beneficial and substantial cardiovascular outcomes were observed and analyzed when compared to the placebo group, therefore, the importance of more promising studies that can corroborate the mitigation of the progression of diabetes kidney disease should be admitted.[7,8]

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Conflicts of interest

The author declares no conflict of interest.

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