Review Article

http://doi.org/10.22265/acnef.4.1.265

How useful in the daily practice of nephrologists are the new antidiabetics with cadiovascular protection?

¿Qué tan útiles en la práctica diaria para los nefrólogos son los nuevos antidiabéticos con protección cardiovascular?

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Abstract
In recent years, several new antidiabetic drugs have been developed, among which only two have demonstrated superiority in cardiovascular protection. They are liraglutide and empagliflozine, which belong, respectively, to GLP-1 RA and SGLT-2i. These medications have also shown benefits in kidney protection. However, in a recent survey of the author among nephrologists in a large colombian city, it has been detected that most do not use these drugs. The greater resistance to the limitation in its use is due to the advanced stages of chronic kidney disease where they are contraindicated, but also to the anawareness of their potential benefits. In this regard, the nephrologists accepted they should learn more about these antidiabetic medicines, because the type of patient that is frequently attended in their consultation will undoubtly benefit, and considering they are obligated to handle the diabetic patient directly.

Key words: liraglutide, empagliflozin, type 2 diabetes, cardioprotection, nephroprotection.

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Resumen
En los últimos años se han desarrollado nuevos fármacos antidiabéticos, entre los que sólo dos han demostrado superioridad en protección cardiovascular. Son liraglutida y empagliflozina, que pertenecen, respectivamente, a los grupos GLP-1 RA y SGLT-2i. Estos medicamentos también han demostrado beneficios en nefroprotección. Sin embargo, en una reciente encuesta del autor entre nefrólogos, en una gran ciudad colombiana, se ha detectado que la mayoría no utilizan estos fármacos. La mayor resistencia a su uso se debe a consideraciones sobre su restricción en etapas avanzadas de la enfermedad renal crónica, pero también al desconocimiento de sus beneficios potenciales. Al respecto, los nefrólogos aceptaron que deberían aprender más acerca de estos medicamentos antidiabéticos, porque el tipo de paciente que frecuentemente asiste a su consulta sin duda se beneficiaría, y más teniendo en cuenta que por el gran número de diabéticos los nefrólogos están obligados a manejar directamente al paciente con esta patología.

Palabras clave: liraglutida, empagliflozina, diabetes tipo 2, cardioprotección, nefroprotección.

http://doi.org/10.22265/acnef.4.1.265

Referenciar este artículo: Villegas Gutiérrez I. ¿Qué tan útiles en la práctica diaria para los nefrólogos son los nuevos antidiabéticos con protección cardiovascular? Rev. Colomb. Nefrol. 2017;4(1): 69 - 73.
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Recibido: 07-12-16 • Aceptado: 19-01-17 • Publicado en línea: 20-02-17

Introduction

Since 2008, FDA[1] introduced the guidelines for the pharmaceutical industry regarding cardiovascular safety (CV) before approving a drug for use in patients with type 2 diabetes mellitus (DM-2), several articles have been published in medical journals high impact. Their results have been variable, always comparing the active drug against a placebo plus the usual standard care, so far resulting such drugs in non-inferior or superior. If this medicine also provides good glycemic control, they are two characteristics that make it the first choice in the management of DM-2. To these drugs with CV protection and good metabolic control is focused this brief analysis of opinion and its relation with the use in nephrological practice.

The antidiabetics analyzed belong to three groups: inhibitors of the enzyme dipeptidyl peptidase 4 (DPP-4i), glucagon-like peptide-1 (GLP 1 RA) receptor agonists and sodium-glucose transporter (SGLT2i) inhibitors. All these studies, in general, have been well planned and comply with a rigorous design in terms of number of patients, inclusion and exclusion criteria, randomization and blinding, and follow-up that, on average, are in 3 years, but a deeper analysis on The differences of each one and that could influence the results, is outside the scope of this short article of opinion. On the other hand, it is expected that in the next four years new studies will be published with other drugs of the three groups mentioned, to complete more than 150,000 patients analyzed.

The first group, DPP-4i, has been presented with sitagliptin (Tecos)[2], saxagliptin (Savor Timi-53)[3] and alogliptin (Examine)[4] studies. With sitagliptin, the results were neutral (non-inferiority), also for alogliptin. However, saxagliptin (also neutral) found a striking decrease in hospitalization for heart failure. Results of the studies of linagliptin (Carmelina[5] and Carolina[6]) are expected over the next three years.

Of the GLP-1 RAs there are three studies presented recently. The first one was with lixisenatide (Elixa)[7], which was neutral. Leader[8] was then presented with liraglutide, which showed a 22% reduction in CV deaths, and which was statistically superior. In the third study, Sustain-6[9], with semaglutide (not yet available in Colombia, at least until 2019), a 39% reduction in nonfatal cerebrovascular disease was found.

Of the SGLT2i, only the Empa-Reg[10] study with empagliflozine has been published, whose results were superior to placebo, decreasing mortality up to 32%.

That is, to date only two studies have shown superiority, the Leader with Liraglutide and the Empa Reg, with empagliflozine. However, both are not strictly comparable, because baseline HbA1c was different, as was the time course of diabetes.

Why are these studies important for nephrologists?

First, because the higher mortality of patients with chronic kidney disease (CKD), even from early stages of the disease, is due to CV causes. Second, because results that demonstrated that metformin decreased CV[11] mortality were published in the 1990s, no new or old antidiabetic drug had demonstrated CV superiority; third because the studies noted here have all been performed against placebo plus the best current standard of care, which means that if superiority is found, this is an extra protection to that already provided by statins, ACE inhibitors or Antagonists of angiotensin II receptors, and good glycemic control. Fourth, and perhaps the most important, the therapeutic arsenal available in CKD is very limited and it is urgently necessary to have new tools for the management of

a pathology that suffers almost 50% of our patients. Thus, in these conditions, finding superiority is an absolutely remarkable fact and provides the nephrological community with new tools for the use in our patients, who are at high risk of mortality from CV disease.

If these drugs that have demonstrated CV superiority are so useful, why is its use among nephrologists so limited?

Compared with other medical specialties (cardiology, endocrinology and internal medicine), nephrologists (at least what can be concluded by a personal survey of the author, in Medellin, Colombia, with few exceptions) have rarely used these antidiabetic drugs, despite Recent resonance studies have had CV superiority, such as Leader and Empa-Reg. The resistance to empagliflozine has to do with the limitation of its use in advanced stages of CKD, since the patients that most treat the nephrologists are those in stages 3 and 4, and empagliflozine is only authorized until the rate of glomerular filtration (GFR) (> 45 mL). Liraglutide is approved for up to 30 mL of GFR, which provides a better profile for use in CKD and, moreover, has already been tested in patients on CKD-5[12] on dialysis, although in small numbers with encouraging results. It is not unreasonable to think that one day the limitation of its use in more advanced stages (CKD 4 and 5) can change.

In terms of decreased HbA1c, empagliflozine on average reduced 0.8-1% and liraglutide up to 1.6%, with insulin being the two most potent antidiabetics13. In the aspect of weight, since patients with CKD are overweight and obese in a high percentage, facts that worsen the CV prognosis, increase the resistance to the action of insulin and decrease the quality of life, the use of liraglutide and empagliflozine Is very beneficial because they lead to an average loss between 3 and 6 kg of weight, being slightly superior with liraglutide[13]. Likewise, the decrease in blood pressure, although it seems insignificant, is not negligible, since, on average, both systolic blood pressure 3-4 mm Hg and diastolic blood pressure 1-2 mm[13] are reduced, and it should be remembered that every 2 mm is decreased The first, the risk of cerebrovascular disease is reduced by 1%.

Regarding the renal benefits specifically, the medications of the three types of molecules have shown variable benefits, which mainly point to a reduction of micro-albuminuria. The Leader study revealed benefits in terms of its decrease, generating a statistically significant result of the renal compound (creatinine doubling, new cases of macro-albuminuria, stage 5 CKD and renal-related mortality)[14]. The same happened with empagliflozine in Empa-Reg Renal[15].

In conclusion, then, we are faced with the surprising and very positive results of two new antidiabetics, liraglutide and empagliflozine, whose clear cardiovascular and renal benefits allow nephrologists to transfer these benefits to our diabetic patients. We should not expect, as subspecialists, to be other physicians outside our groups who always prescribe the diabetic patients we treat. We must actively manage very clear concepts regarding CV benefit and impact on glycemic control, renal function, weight and blood pressure, and to know if renal stage contraindicates or allows its use. Finally, one must be very emphatic in not extrapolating benefits to populations different from those analyzed in the mentioned studies; however, the good news for nephrologists is that the inclusion criteria in those studies strongly resemble patients in our daily practice and hence the call to have them present.

Ethical Responsibilities

Protection of people and animals

The authors state that no human or animal experiments have been performed for this research.

Confidentiality of data

The authors state that no patient data appears in this article.

Right to privacy and informed consent

The authors state that no patient data appears in this article.

Interest conflict

The author declares that there is no conflict of interest.

Article published without funding.

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