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Letter to the Editor

# Earlier onset of treatment improves the nephroprotective effect of dapagliflozin

## El inicio temprano del tratamiento mejora el efecto nefroprotector con dapagliflozina

*Dear Editor,*

Chronic kidney disease (CKD) is a common condition that is a major risk factor for cardio-vascular events, end-stage renal disease and all-cause mortality.[1] In several large trials, dapagliflozin treatment reduced both primary and secondary renal outcomes at different levels of estimated glomerular filtration rate (eGFR). Dapagliflozin reduced the rate of eGFR decline over time, one of the secondary renal outcomes. [2–5]

Glomerular hyperfiltration plays a key role in the progression of CKD, causing intraglomerular hypertension, inflammatory changes, extracellular matrix accumulation and podocyte injury. In addition, loss of eGFR causes compensatory hyperfiltration in the remaining nephrons, leading to further decline in eGFR through glomerulosclerosis and tubulointerstitial fibrosis. Sodium-glucose linked transporter type 2 (SGLT-2) inhibitors are associated with a reduction in glomerular hyperfiltration, probably due to an increase in preglomerular vasoconstriction and a decrease in postglomerular vascular resistance.[6]

We therefore investigated whether the efficacy of dapagliflozin in slowing the progression of eGFR decline would be influenced by the degree of renal function. A well-known phenomenon observed in studies performed with SGLT-2 inhibitors is a more pronounced fall of the eGFR in treated groups than in PBO groups during the first weeks of treatment (acute phase). This was followed by a partial recovery and thereafter a persistent lower decline of the

**Table 1 – Differences between DAPA and PBO groups in time lapse (years) from eGFR at onset of chronic phase to ESKD.**

| Studies | eGFR at onset of chronic phase | eGFR reserve to ESKD | eGFR decline per year in chronic phase | eGFR decline per year in chronic phase PBO-DAPA | Time to ESKD differences DAPA vs. PBO |
|---|---|---|---|---|---|
| *DECLARE-TIMI 58 kidney disease prevention post hoc analyses*[8] | | | | | |
| DAPA | 82.41 | 67.41 | 1.54 | 1.01 | 68.27 |
| PBO | 83.95 | 68.95 | 2.55 | | |
| *DAPA-HF renal function outcomes*[9] | | | | | |
| DAPA | 61.81 | 46.81 | 1.09 | 1.76 | 28.07 |
| PBO | 64.41 | 49.41 | 2.85 | | |
| *DAPA-CKD prespecified analysis*[4] *eGFR > 45* | | | | | |
| DAPA | 51.80 | 36.80 | 1.99 | 2.14 | 18.27 |
| PBO | 54.10 | 39.10 | 4.13 | | |
| *DAPA-CKD prespecified analysis*[4] *eGFR < 45* | | | | | |
| DAPA | 32.10 | 17.10 | 1.48 | 1.74 | 10.8 |
| PBO | 33.80 | 18.80 | 3.22 | | |
| *DELIVER kidney outcomes prespecified analysis*[7] | | | | | |
| DAPA | 57.3 | 42.3 | 0 | 1.4 | 32.57 |
| PBO | 60.6 | 45.6 | 1.4 | | |

Data taken from referred studies. eGFR: estimated glomerular filtration rate (ml/min/1.73 $m^2$); ESKD: end stage kidney disease; DAPA: dapagliflozin; PBO: placebo.

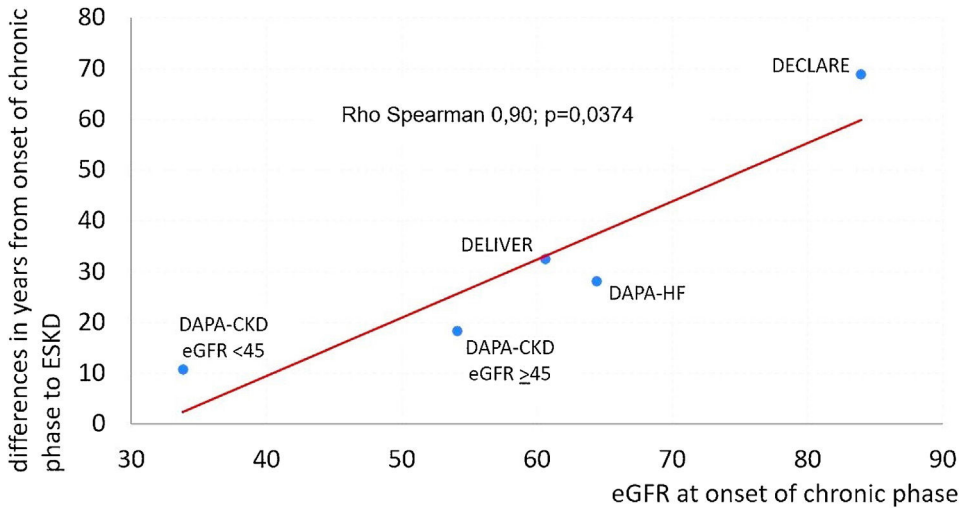


**Fig. 1 – Correlation between eGFR at onset of chronic phase and differences in time lapse (years) from onset of chronic phase to ESKD. Data taken from referred studies. eGFR: estimated glomerular filtration rate (ml/min/1.73 m$^2$); ESKD: end stage kidney disease; DAPA: dapagliflozin; PBO: placebo.**

eGFR until the end of the follow-up period (chronic phase) in treated groups. Thus, for the present analysis we took data from several published studies[4,7–9] to evaluate the possible existence of a correlation between eGFR at the onset of chronic phase and differences in time to end stage kidney disease (ESKD). The eGFR reserve to ESKD was calculated as eGFR at onset of chronic phase minus 15. The difference in time to ESKD induced by dapagliflozin intervention was calculated by dividing the eGFR reserve to ESKD in the placebo group by the PBO-DAPA difference in eGFR decline per year during the chronic phase (Table 1). As a result, we found a significant correlation between these two parameters (Rho Spearman 0.90; $p = 0.0374$) (Fig. 1).

In view of this finding, we believe that it is reasonable to conclude that the nephroprotective effect of dapagliflozin could be related to the degree of renal function. It could be said that from a mechanistic point of view this is not an unexpected finding, since the smaller the mass of functioning nephrons, the fewer the number of points at which the drug can exert its mechanism of action. This may have broad applicability in the clinical setting because although dapagliflozin could delay the disease progression at any stage of CKD, the earlier treatment is established the longer the patient will remain in a less unfavourable clinical condition. Thus, the early initiation of treatment is of particular interest, not only because of its clinical relevance, but also because it can result in substantial cost savings both in terms of reduced pharmaceutical costs and a smaller number of patients on renal replacement therapy.

## Conflict of interest

Antonio Gippini has received fees for presentations and advisory boards from Amgen, AstraZeneca, Boehringer-Ingelheim, Esteve, Ferrer, Janssen, Lilly, Mundipharma, Mylan, Novartis and NovoNordisk.

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# Experiencia en vida real con terapias frente a COVID-19 leve-moderada en trasplantados renales: ¿cómo tratar a partir de ahora a los pacientes con enfermedad renal crónica?

## Real-world experience with mild-moderate COVID-19 therapies in kidney transplant patients: How to treat patients with chronic kidney disease from now on?

*Sr. Director,*

En los últimos meses, las recomendaciones para el tratamiento de pacientes no hospitalizados con COVID-19 leve-moderada con alto riesgo de progresión a enfermedad grave incluían varios fármacos antivirales (nirmatrelvir/ritonavir, remdesivir y molnupiravir) y anticuerpos monoclonales (mAB) (fundamentalmente sotrovimab en Europa)[1]. Sin embargo, hay poco documentado sobre su eficacia en vida real en receptores de trasplante renal (TR)[2,3].

Realizamos un estudio de cohortes retrospectivo de todos los TR con COVID-19 leve-moderada durante el periodo del 1 de enero de 2022 al 31 de diciembre de 2022 que recibieron tratamiento ambulatorio en nuestra área hospitalaria. Definimos COVID-19 leve-moderada cuando los pacientes presentaban síntomas relacionados con la infección por SARS-CoV-2 (diagnosticada por PCR y/o antígeno) sin indicación de ingreso hospitalario. Consideramos progresión a COVID-19 grave cuando los pacientes requirieron hospitalización y/o fallecieron. La indicación de tratamiento farmacológico se realizó según factores de riesgo conocidos de progresión de la enfermedad: edad >60 años y/o tiempo post-TR <2 años y/o comorbilidades. La elección del fármaco dependió de los títulos de IgG anti-S (<1.000 BAU/ml: sotrovimab) y del filtrado glomerular estimado (FGe) (>30 ml/min/1,73 $m^2$: remdesivir en pauta de 3 días; <30 ml/min/1,73 $m^2$: molnupiravir). No consideramos utilizar nirmatrelvir/ritonavir debido a las fuertes interacciones farmacológicas descritas con los fármacos inmunosupresores. Por otro lado, recogimos datos de todos los pacientes TR que requirieron hospitalización por COVID-19 durante el periodo del estudio, tanto los tratados como los no tratados antes del ingreso, como grupo de comparación.

Durante 2022, 107 TR con COVID-19 leve-moderada recibieron tratamiento ambulatorio (sotrovimab n = 63, remdesivir n = 34, molnupiravir n = 10) (tabla 1). El 83,8% estaban vacunados según la pauta indicada por el Ministerio de Sanidad en el momento de la infección. No había diferencias en las características de los pacientes ni en las manifestaciones clínicas según el fármaco recibido, salvo en los criterios de indicación de cada fármaco (función renal, IgG anti-S).

Por otro lado, 37 TR fueron hospitalizados a lo largo del año por COVID-19. Solo 3 de ellos habían recibido tratamiento ambulatorio previamente (sotrovimab n = 2, molnupiravir n = 1); el resto no contactaron previamente con la consulta de TR y ya presentaban COVID-19 grave cuando acudieron al hospital, precisando ingreso. Al comparar los factores de riesgo reconocidos para la progresión a COVID-19 grave, no encontramos diferencias entre los dos grupos, tratados y no tratados de forma ambulatoria (tabla 2). Cinco pacientes fallecieron, todos ellos del grupo que no había recibido tratamiento ambulatorio.

Presentamos la serie más extensa de pacientes TR con COVID-19 leve-moderada tratados de forma ambulatoria. Nuestros resultados sugieren que las terapias anti-COVID-19 en fase temprana pueden detener la progresión a enfermedad grave en pacientes de alto riesgo. Muy pocos pacientes de los tratados ambulatoriamente precisaron ingreso y ninguno falleció. Los pacientes ingresados sin tratamiento previo