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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.

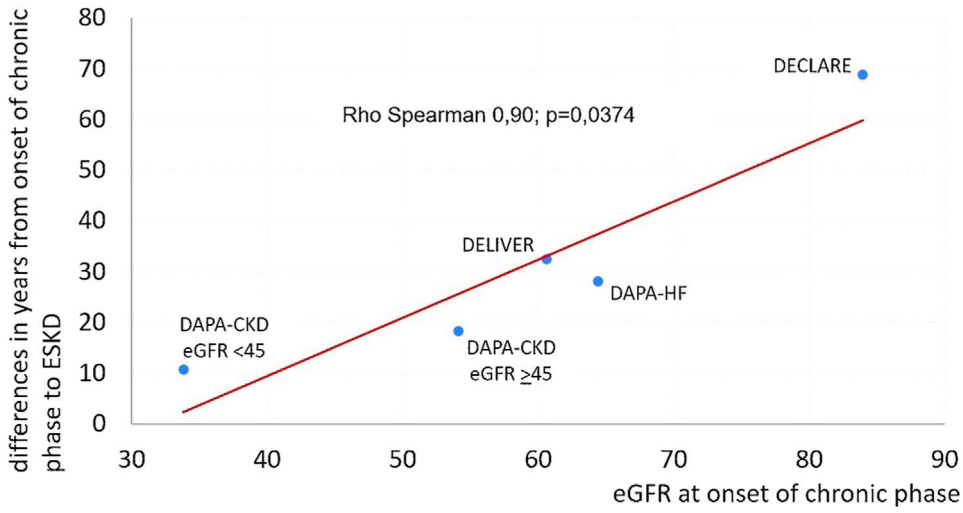

Fig. 1 – Correlation between eGFR at onset of chronic phase and differences in time lapse (years) from onset of chronic phase to ESKD. Data taken from referred studies. eGFR: estimated glomerular filtration rate (ml/min/1.73 m^2); ESKD: end stage kidney disease; DAPA: dapagliflozin; PBO: placebo.

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

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

Dear Editor,

In recent months, recommendations for the treatment of non-hospitalized patients with mild-moderate COVID-19 and high risk of progression to severe disease included several antiviral drugs (nirmatrelvir/ritonavir, remdesivir and molnupiravir) and monoclonal antibodies (mAB) (primarily sotrovimab in Europe).[1] However, there is little documented real-life efficacy in renal transplant (RT) recipients.[2,3]

We conducted a retrospective cohort study of all RTs with mild-moderate COVID-19 during the period January 1, 2022, to December 31, 2022, who received outpatient treatment in our hospital area. We defined mild-moderate COVID-19 when patients had symptoms related to SARS-CoV-2 infection (diagnosed by PCR and/or antigen) without an indication for hospital admission. We defined severe COVID-19 if patients required hospitalization or died. The indication for drug treatment was made according to known risk factors for disease progression: age > 60 years and/or post-RT time < 2 years and/or comorbidities. The choice of drug depended on anti-S IgG titers (< 1.000 BAU/ml: sotrovimab) and estimated glomerular filtration rate (eGFR) (>30 ml/min/1.73 m^2: remdesivir in 3 day regimen; <30 ml/min/1.73 m^2: molnupiravir). We did not consider using nirmatrelvir/ritonavir because of the strong drug interactions described with immunosuppressive drugs. Additionally, we collected data from all RT patients requiring hospitalization for COVID-19 during the study period, both treated and untreated prior to admission, as the comparison group.

During 2022, 107 RT patients with mild-moderate COVID-19 received outpatient treatment (sotrovimab n = 63, remdesivir n = 34, molnupiravir n = 10) (Table 1). A total of 83.8% were vaccinated at the time of infection according to guidelines provided by Ministry of Health. There were no differences in patient characteristics or clinical manifestations in relation to the drug received, except for the indication criteria for each drug (renal function, anti-S IgG).

In addition, 37 RT patients were hospitalized throughout the year for COVID-19. Only 3 of them had previously received outpatient treatment (sotrovimab n = 2, molnupiravir n = 1); the rest did not previously contact their RT doctor and already had severe COVID-19 when they attended the hospital, requiring admission. When comparing the recognized risk factors for progression to severe COVID-19, we found no differences between the two groups, treated and not treated, on an outpatient basis (Table 2). Five patients died, all of them in the group that had not received outpatient treatment.

We present the largest series of RT patients with mild-moderate COVID-19 treated on an outpatient basis. Our results suggest that early anti-COVID-19 therapies can halt the progression to severe disease in high-risk patients. Very few of the patients treated as outpatients required admission and none died. Patients admitted without prior treatment had risk factors for the development of severe COVID-19 similar to those in the outpatient group. Considering the favorable evolution

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