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Paricalcitol for pre-dialysis stages of chronic kidney disease

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To the Editor,

After having read the interesting article by Dr Hervás Sánchez et al on the effectiveness of treatment with paricalcitol in patients with pre-dialysis chronic kidney disease,[1] we would like to take the time to make a few comments.

This study correctly describes the results obtained in controlling hyperparathyroidism and meeting the calcium, phosphorus and parathyroid hormone (PTH) target values recommended by the S.E.N. and KDOQI guidelines.[2] The study was undertaken in normal clinical practice conditions with a retrospective analysis of 92 patients in stage 3 or 4 CKD, and the conclusion was that treatment with paricalcitol was effective for meeting the target values.

However, the data analysis section includes a piece of information that the authors did not comment at all. Levels of 25-OH vitamin D in their population were quite deficient, as occurs frequently in such cohorts.[3] Mean recorded levels were 16.2±8ng/ml and 75% had levels below 21ng/ml.

We would like to issue a reminder that both the KDOQI and S.E.N. 2011 guidelines recommend starting native vitamin D treatment if 25-OH D levels are below 30ng/ml, and they only indicate treatment with active vitamin D if PTH values exceed the established target once 25-OH D levels have been normalised.

This aspect is relevant for two reasons:

1. From a clinical viewpoint, it is important to reach the right plasma levels of 25-OH vitamin D. By doing so, we will achieve better control over hyperparathyroidism, in addition to an array of other effects that we will not list in this brief discussion. This is also true in stage 5 chronic kidney disease,[4] but it is especially relevant in earlier stages, such as those in the study in question. This does not mean that paricalcitol cannot be indicated as treatment for bone and mineral metabolism disorders, but it should not be used as a first-line treatment.

2. The economic impact of this decision is considerable. The estimate cost of treatment with native vitamin D is 20 to 30 Euros per patient per year, while treatment with paricalcitol may be more than 1700 Euros yearly. And in the range of different vitamin D receptor activators, some options are much more economical and have also been shown to be equally effective.[3] This reflection is especially relevant now that the sustainability of our health system is a matter for concern, in fact, many editorial comments have been published on the subject, both in Spain and internationally.[5]

Without a doubt, the most important consideration is benefit to the patient, and to achieve this, we should follow the recommendations in the guidelines.

Conflicts of interest

The authors affirm that they have no conflicts of interest related to the content of this article.

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Response to "Paricalcitol for pre-dialysis stages of chronic kidney disease"

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To the Editor,

We were very interested by the comments submitted by Drs Almirall and Bolos from *Corporació Sanitària i Universitària Parc Taulí* at Hospital de Sabadell (Barcelona), regarding our article on the effectiveness of paricalcitol for controlling hyperparathyroidism in early stages of chronic kidney disease,[1] and first of all, we would like to thank them for their input.

They are completely correct in pointing out that we did not highlight the relevant fact that the level of 25-OH vitamin D was deficient in our patient population. We did not call attention to this fact because we are currently undertaking a larger study on vitamin D deficiency, including more than 300 patients with chronic kidney disease (CKD) in pre-dialysis stages, and given the scope and length of this article, we decided –perhaps erroneously– to leave it for a later occasion.

However, we would like to comment on some of the ideas expressed by these authors, with a particular view to compensate for the lack of information on vitamin D that they detected.

First of all, levels of both native vitamin D and calcitriol are low in CKD, and the complex relationships between them are still largely unclear. This is also reported by Dr Dusso in a recent article[2] regarding both the calcium-parathyroid hormone-bone axis and their so-called pleiotropic effects due to vitamin D receptors being widespread. It is interesting to note that CKD patients may have a vitamin D deficiency of up to 80%, even though the conversion to 25-OH vitamin D by 25-hydroxylase (CYP2R1) occurs in the liver and not the kidney.[3]

In addition, the cause of 25-OH D deficiency is unclear. Hypotheses include low exposure to sunlight, deficient intake of provitamin and many more. We know that calcidiol binds to DBP (vitamin D binding protein), and is filtered by the glomerulus, and is later endocytosed via megalin into proximal tubule cells. It has been demonstrated that disease progression in renal patients is accompanied by a decrease in megalin. At the same time, there may be a loss of DBP and even 25-OH vitamin D in proteinuric kidney disease. Furthermore, 25-OH D deficiency is very common in nephrotic syndrome, even when renal function is normal. Similarly, in early stages of kidney disease, increased FGF 23 may inhibit activity by renal 1-alpha hydroxylase and increase catabolism of 1,25-D and 25-OH D, thereby activating production of the enzyme that breaks down both forms (24-hydroxylase). It has even been observed that calcium deficiency promotes depletion of 25-OH D. In addition, 1,25-D itself stimulates hepatic inactivation of 25-OH D.[4] We therefore completely agree with treating and maintaining proper 25-OH D levels from stage 1-2 kidney disease, as recommended by the S.E.N. 2011 guidelines.

However, a different issue is whether vitamin D supplements alone are sufficient to control hyperparathyroidism. It seems obvious that proper levels of 25-OH D, the substrate for calcitriol synthesis, must be reached in order to promote the synthesis process and prevent hyperparathyroidism. Nevertheless, it is unlikely that vitamin D supplements are enough to compensate for low VDR expression in tissues. It has been reported that using ergocalciferol as a supplement reduces PTH only in those patients with serum levels of 25 OH-D below 30ng/ml.[2] It has also been reported that only 50% of patients with stage 3 or 4 CKD who take vitamin D supplements see an increase in 25-OH D levels.[5]

In any case, we feel that the matter is open for debate. Preclinical and clinical trials with sufficient prospective power should be undertaken in order to determine the benefit in simultaneously providing vitamin D supplements and active metabolites of vitamin D. However, although Dr Dusso warns of the risk of toxicity associated with this combination and it does not seem recommendable at present.[2]

Lastly, regarding the economic savings associated with using a certain treatment or another (which is certainly a hot topic today), our attention was called to the last sentence in the letter, which reminds us that the most important consideration is the benefit to the patient. Public prices are established by the authorities which regulate and shape healthcare policy, and not by doctors. We believe that our role is to make efficient use of the resources which the Health System puts at our disposal and choose the best option for each patient and each specific situation. This will be the case as long as we are permitted to make choices, because given the current climate, it is likely that only one drug will be provided for treating a condition in the near future, and that it will be chosen by political