Targeting NaPi-IIb for Hyperphosphatemia in Chronic Kidney Disease Patients - The Dead End?

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Phosphate serves as a structural component of nucleic acids, cell membranes and bones, and is important for enzymatic interactions, ATP synthesis and plays a critical role in cellular signalling through phosphorylation reactions. Therefore, the maintenance of phosphate balance is essential for life being tightly regulated by a sophisticated system in humans, involving intestinal uptake of dietary inorganic phosphate (Pi), storage in bone and excretion of excess Pi in the kidney. However, due to the dependence of phosphate elimination on urinary excretion by the kidneys, patients with decreased kidney function are likely to be in a positive phosphate balance. The resulting hyperphosphatemia has been well recognized as a crucial factor in the pathogenesis of mineral and bone disorders associated with chronic kidney disease, being also associated with increased risks of death and cardiovascular complications.1,2

Regular monitoring and prevention of hyperphosphatemia is therefore universally recommended in clinical guidelines,3 although normalization of serum phosphate with phosphate binders with concurrent dietary measures in dialysis patients remains challenging. Furthermore, the use of phosphate binders is also frequently accompanied by gastrointestinal side effects and poor patient compliance, which limits their use and underscores the need for additional therapeutic options.3 Although phosphate binders are the mainstay of pharmacological therapy, lowering phosphate levels by targeting the intestinal phosphate absorption seems an interesting approach. Drugs that actively target gastrointestinal phosphate transport combined with phosphate-binder therapy could optimize the therapeutic effects of both treatments and enhance the effectiveness of dietary phosphate restriction. The discovery nearly two decades ago of the sodium-dependent phosphate co-transporter type 2b (NaPi-IIb) which mediates active phosphate absorption in the small intestine4 opened the road of studying different molecules oriented toward NaPi-IIb inhibition as a target for hyperphosphatemia treatment.

In the latest number of Kidney Int. Reports, Maruyama S. et al. presents the results of a 2-part, randomized, placebo- and active-controlled, single- and repeated-dose, phase 1b study evaluating the safety and efficacy of DS-2330, for the treatment of hyperphosphatemia in haemodialysis patients.5 DS-2330b is an oral NaPi-IIb inhibitor that inhibits the uptake of phosphate via NaPi-IIb in the small intestine in animal and ex vivo studies, resulting in reduced intestinal phosphate absorption.

In their comprehensive study, Maruyama S. et al demonstrated that DS-2330, either alone or in combination with sevelamer was generally well tolerated with no concerning safety signals. However, DS-2330b produced only a small decrease in serum phosphate either as a single agent or in combination with sevelamer therefore raising concerns about efficacy of this molecule in controlling hyperphosphatemia in patients on haemodialysis. The lower plasma concentration of DS-2330 in patients concomitantly receiving sevelamer compared to DS-2330b alone along with a higher reduction in serum phosphate among sevelamer with placebo treatment group suggest a possible competing effect between sevelamer DS-2330b for phosphate binding sites, causing a reduction in bioavailability of DS-2330b.

Other clinical approaches with other oral inhibitors of active phosphate transport modulating NaPi-IIb have also yielded disappointing results. Thus, a recent clinical trial in end-stage renal disease patients revealed that another selective NaPi-IIb inhibitor - ASP3325 neither
inhibited intestinal phosphate absorption nor ameliorated hyperphosphatemia or provide a reduction in phosphate metabolism biomarkers.6

Nicotinamide, a metabolite of nicotinic acid (niacin, vitamin B3), is a marketed drug with anti-inflammatory and cholesterol-lowering properties; in addition it may lower phosphate levels by a mechanism involving negative transcriptional regulation of NaPi-IIb in the intestine. Despite some promising result in some clinical studies,7,8 a more recent randomized controlled trial found that nicotinamide and sevelamer were equally effective in lowering phosphate levels in CKD patients but with the price of a more adverse events in the nicotinamide arm resulting in a higher discontinuation rate.9

Taken together, the results of these studies suggest a limited effect of NaPi-IIb inhibitors for the treatment of hyperphosphatemia in CKD patients. This lack of effect may be due to the decreased NaPi-IIb intestinal expression in advanced CKD as suggested by a recent experimental study; this suggests that other alternative phosphate transporter may predominate in the setting of advanced kidney disease.10 Thus, low-affinity transporters, such as PiT-1 or PiT-2 gain importance for intestinal phosphate absorption; inhibition of these transporters might represent a novel therapeutic approach to ameliorate hyperphosphatemia in kidney diseases.

Phosphate is actively absorbed in the small intestine via the above described transporters but also passively via the tight junctions between cells (i.e. paracellular).51 The later represents the target of tenapanor, a minimally absorbed inhibitor of gastrointestinal sodium/hydrogen exchanger 3 (NHE3); it acts via a non-phosphate-binding mechanism, reducing paracellular phosphate transport in the intestine. In a phase 3 randomized, double-blind trial, tenapanor significantly reduced serum phosphate compared with placebo at eight weeks in patients receiving hemodialysis. Tenapanor is a minimally absorbed compound with detectable levels in serum only rarely being described, its administration being also associated with a dramatic reduction in pill burden when compared with commonly used doses of phosphate binders. Adverse effects were limited to a modest increase in stool frequency, thought to be due an increase in stool water content, which led to drug discontinuation in 8 percent of those treated.

Although the relative contribution of the active versus passive pathway remains unknown, a pan-phosphate transporter inhibitor would therefore represent a better alternative to control hyperphosphatemia in CKD patients. In this regard, a novel inhibitor, EOS789, that interacts with several sodium-dependent phosphate transporters (NaPi-IIb, PiT-1, and PiT-2) markedly decreasing the serum phosphate, fibroblast growth factor-23, and intact parathyroid hormone in rats.52 Thus, this novel approach might provide a significant benefit to patients who are ineffectively treated with phosphate binders. However, extrapolating these results from rodents to humans remains an open question; studies using human intestine are required to elucidate the expression levels of phosphate transporters.

DISCLOSURE
The authors declared no competing interests.

SUPPLEMENTARY MATERIAL
Supplementary File (PDF)
Supplementary References.

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