REVIEW ARTICLE

New Directions in Phosphorus Management in Dialysis

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Current phosphate management strategies in end-stage renal disease (dietary phosphate restriction, dialysis, and phosphate binders) are inadequate to maintain target phosphate levels in most patients. Dietary phosphate restriction is challenging due to "hidden phosphates" in processed foods, and dialysis and phosphate binders are insufficient to match average dietary phosphate intake. As phosphate binders must be taken with each meal, patients need to ingest many, large pills several times a day, negatively impacting quality of life. Recent advances in our understanding of phosphate absorption pathways have led to the development of new nonbinder therapies that block phosphate absorption. This review describes the limitations of current phosphate management strategies and discusses new therapies in development that inhibit phosphate absorption pathways. These new therapies present an opportunity to rethink phosphate management, potentially by prescribing phosphate absorption inhibitors as a primary therapy and adding phosphate binders if needed.

Introduction

THE MANAGEMENT OF hyperphosphatemia in end-stage renal disease (ESRD) has centered around the dietary restriction of phosphorus, removal of phosphorus using dialysis, and binding phosphorus to prevent absorption by the gastrointestinal tract using phosphorus binders.[1] However, these approaches are all limited. First, we live in an era where our diet contains high amounts of "hidden phosphates" from food additives, making dietary restriction of phosphorus in the traditional sense difficult and unreliable. Based on data from nutritional databases, average phosphate intake in the modern Western diet is ~1,400 mg/day,[2] but these databases have been shown to underestimate actual phosphate quantities.[3] Moreover, phosphate additives can contribute an additional ~1,000 mg/day.[4] Thus, daily phosphate intake in a typical Western diet may approach ~2,400 mg/day, more than 300% of the recommended daily allowance of 700 mg.[5] Of course, the maximum amount of phosphate that can be removed by dialysis or bound by binders is limited.[6-8] Our current inability to consistently achieve recommended target phosphorus levels in the majority of patients on dialysis argues for the need for innovations in phosphate management.[9]

The recent development of novel compounds to block phosphorus absorption affords us the chance to rethink our approach to the management of hyperphosphatemia, given the mechanistic understanding of phosphate absorption. Therapies with mechanisms that directly target the absorption of phosphorus rather than chemically binding it are being developed. This approach is notably different than that of currently available phosphate binders. One class of such therapies is inhibitors of sodium-dependent phosphate cotransporter type 2b (NaPi2b, also called SLC34A2) (e.g., ASP3325).[10,11] Another that was more recently developed is the sodium-hydrogen exchanger 3 (NHE3) inhibitor tenapanor.[12] Inhibition of NHE3 may prove to be a useful therapeutic strategy for phosphate control, given the evidence that the NHE-mediated paracellular phosphate absorption pathway is the dominant site of intestinal phosphate absorption in humans.[13,14] In this review, we discuss the limitations of current phosphate management approaches and describe new, targeted, nonbinder therapies that have been developed.

Mechanisms of Phosphate Absorption and the Role of the Paracellular Pathway

Dietary phosphate absorption occurs in the gastrointestinal tract via 2 distinct mechanisms, namely the transcellular and paracellular pathways. Active transcellular phosphate transport occurs primarily through the NaPi2b.[15] Davis et al.[14] demonstrated that active transport saturates at a luminal phosphate concentration of ~6 mg/dL

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Financial Disclosure: Editorial support provided by Ardelyx, Inc. J.P.D. reports consulting fees from Ardelyx and Akebia. E.K. reports consulting fees from Ardelyx, Vifor, and Otsuka.

Support: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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1051-2276

https://doi.org/10.1053/j.jrn.2022.04.006

(~2 mmol/L) and that this pathway mediates phosphate absorption when phosphate concentrations are low. Passive paracellular diffusion occurs along concentration gradients through tight junction complexes between cell membranes.[16] This pathway does not saturate and is responsible for the majority of intestinal phosphate absorption when luminal phosphate concentrations are high.[14,16] It is estimated that transcellular transport accounts for 20-35% of total intestinal phosphate absorption, and paracellular diffusion constitutes 65-80%.

The bulk of evidence suggests that the primary mechanism of phosphate absorption in the gastrointestinal tract for individuals with Western diets is the paracellular pathway, not the transcellular pathway. Although the NaPi2b inhibitor ASP3325 effectively reduced phosphate concentrations in rats with renal failure,[10] no changes in serum, urinary, or fecal phosphate were observed in human trials of healthy volunteers or hyperphosphatemic ESRD patients, irrespective of dose.[13] EOS789, a pan-inhibitor of NaPi2b, pituitary-specific positive transcription factor 1, and pituitary-specific positive transcription factor 2, reduced fractional phosphate absorption compared to placebo in a phase 1 study, but the efficacy of this molecule has not been evaluated in phase 2 and 3 studies.[17] A targeted NHE3 inhibitor effectively reduced paracellular phosphate absorption and decreased urinary phosphate excretion in an animal model and lowered phosphate concentrations in human trials.[12,18]

Novel Molecules in Development Target Paracellular Uptake of Phosphate in the Gastrointestinal Tract

Tenapanor, an investigational first-in-class NHE3 inhibitor, produces modest intracellular proton retention which is proposed to induce conformational change(s) in claudin proteins present in tight junctions, thereby reducing paracellular phosphate absorption[12] (Fig. 1). By reducing paracellular phosphate absorption, tenapanor directly and efficiently reduces serum phosphorus concentrations.[12] The long-term efficacy and safety of tenapanor as monotherapy was studied in a 1-year trial of patients with ESRD on dialysis.[20] Subjects who experienced an increase in serum phosphorus of at least 1.5 mg/dL after the washout period of up to 4 weeks and who had a post binder washout baseline phosphorus concentration between 6 and 10 mg/dL were randomized to receive tenapanor (30 mg twice daily) or sevelamer (per label) as an active safety control.[20] After a 26-week treatment period, subjects randomized to tenapanor entered a 12-week withdrawal period in which they were randomized to continue treatment with tenapanor or switch to placebo.[20] The primary outcome of this study was the difference in change in phosphate concentrations between the pooled tenapanor-treated patients and the placebo-treated patients in the efficacy analysis set (defined as patients with at least a 1.2 mg/dL decrease in serum phosphorus concentration over the randomized treatment period) from the beginning to the end of the withdrawal period.[20] The trial met its primary outcome, with the least-squares mean difference in phosphorus concentration change between tenapanor and placebo of −1.4 mg/dL ($P < .0001$) in the efficacy analysis set.[20]

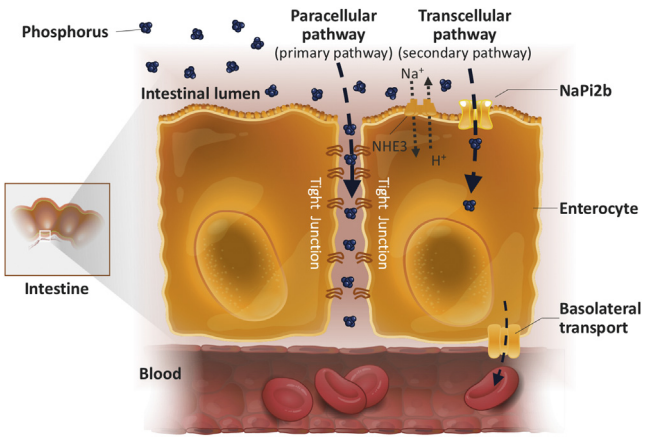

Figure 1. Illustration of phosphate absorption pathways. NaPi2b, sodium-dependent phosphate cotransporter type 2b.[19]

Mean serum phosphorus concentrations decreased from 7.7 mg/dL at baseline to 5.1 mg/dL at the end of the 26-week randomized treatment period in the efficacy analysis set, a mean decrease of 2.6 mg/dL.[20] In the tenapanor intent-to-treat analysis, 77% of subjects demonstrated a clinical response (defined as a decrease in serum phosphorus of ≥0.1 mg/dL) with a mean decrease of 2.0 mg/dL.[20] The only adverse event reported by more than 5% of patients on tenapanor was diarrhea (53% of patients during the randomized treatment period).[20] However, diarrhea was typically transient and mild-to-moderate in severity.[20] The majority of patients who experienced diarrhea continued treatment (68.9%).[20] Rates of serious adverse events were higher in patients treated with sevelamer carbonate (16.4-23.4%) compared to tenapanor (11.2-17.4%) across all study periods.[20] Three phase 3 studies have been completed thus far. The sponsor of tenapanor (Ardelyx, Inc, Fremont, CA) has received a complete response letter from the Food and Drug Administration regarding the New Drug Application for tenapanor and is pursuing options for obtaining approval.

Previous Clinical Trials for Other Phosphate-Lowering Therapies

Other trials to test efficacy of phosphate binders have used similar study design. The second phase 3 trial of ferric citrate in ESRD employed a similar study design in which the primary outcome compared the effect of ferric citrate to placebo.[21] After a binder washout period, subjects on dialysis were randomized to receive ferric citrate or active

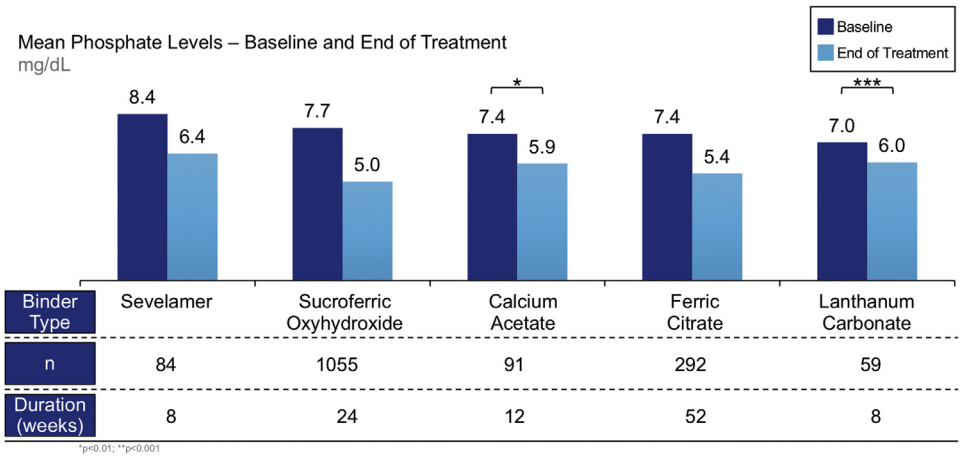

Figure 2. Efficacy of phosphate binders in their phase 3 trials.[22,24-27]

control (sevelamer and/or calcium acetate) during the 52-week safety assessment period, followed by a 4-week placebo-controlled efficacy assessment period.[21] The primary endpoint was the difference in serum phosphorus concentrations in ferric citrate versus placebo during the efficacy assessment period.[21] Mean baseline phosphorus was similar in the 2 arms at the beginning of the efficacy assessment period (ferric citrate: 5.1 mg/dL; placebo: 5.4 mg/dL) and lower in the ferric citrate group by the end (ferric citrate: 4.9 mg/dL; placebo: 7.2 mg/dL), with an adjusted mean difference of 2.2 mg/dL ($P < .001$).[21]

In contrast, other recent phosphate binder trials have been designed to demonstrate noninferiority to active control. Floege et al. evaluated sucroferric oxyhydroxide versus sevelamer carbonate over 24 weeks in subjects on dialysis with hyperphosphatemia.[21] Serum phosphorus concentrations decreased from 7.7 mg/dL at baseline to 5.3 mg/dL in the sucroferric oxyhydroxide and 7.4 mg/dL to 5.0 mg/dL in the sevelamer carbonate at week 24.[22] Another phase 3 trial compared the same therapies for phosphate management in patients with chronic kidney disease on dialysis over a 12-week treatment period.[23] Noninferiority of sucroferric oxyhydroxide to sevelamer carbonate was demonstrated in both trials.[22,23] Figure 2 summarizes the primary outcomes of the approved phosphate binders in the United States.

Dietary Phosphorus Content Overwhelms Typical Options for Phosphorus Control

Dietary phosphate restriction is complicated by the high amounts of "hidden" phosphate additives in the modern diet, which contribute significantly to the overall phosphate burden.[28] Given that a modern diet is high in processed foods containing large amounts of phosphate additives, the normal daily phosphate intake is estimated to exceed 2,500 mg/day.[29,30] Some patients on dialysis may have no choice but to consume processed foods. An estimated 17% of the US population, or approximately 54 million people, live in low-income and low-access areas far from supermarkets,[31] so they likely need to rely on highly processed foods due to the lack of readily available healthy, fresh groceries. Current phosphate intake is more than 300% of the recommended dietary allowance.[5,32] Dialysis is said to remove <20% of the phosphorus consumed, so binders were developed to make up for this difference.[6] It should be noted that thrice-weekly in-center nocturnal hemodialysis was shown to result in a statistically significant decline in phosphorus levels from 5.7 to 5.0 mg/dL ($P < .001$).[33] However, the time commitment per session (mean of 7.9 hours)[33] and the requirement to stay in a dialysis center overnight may make this option impractical and unpleasant for many patients.

Limitations to the Current Approach to Phosphorus Control in End-Stage Renal Disease

Phosphate binders, as a class, generally cannot achieve and maintain guideline recommended phosphorus concentrations <5.5 mg/dL[21,24-26,33] (Fig. 2). Phosphate binders work by binding phosphate in the gastrointestinal tract to create nonabsorbable compounds that are then excreted.[24-27] This mechanism of action is inefficient because binders do not target either of the phosphate absorption pathways[34-38] and, importantly, do not target/directly act on the paracellular pathway, which is the primary site of phosphate absorption.[14] In vivo binding capacities for binders have been found to range from 21 to 135 mg phosphate per capsule/tablet. Limited binding capacity per pill leads to the requirement for large and/or many pills (and pill burden increases as intake increases).[34-38] The intrinsic mechanism of action implies a short duration of action that leads to the requirement that binders need to be taken every time the patient eats (e.g., with each meal/snack) to bind the phosphorus in that individual meal.[34-38] Off-target binding, while

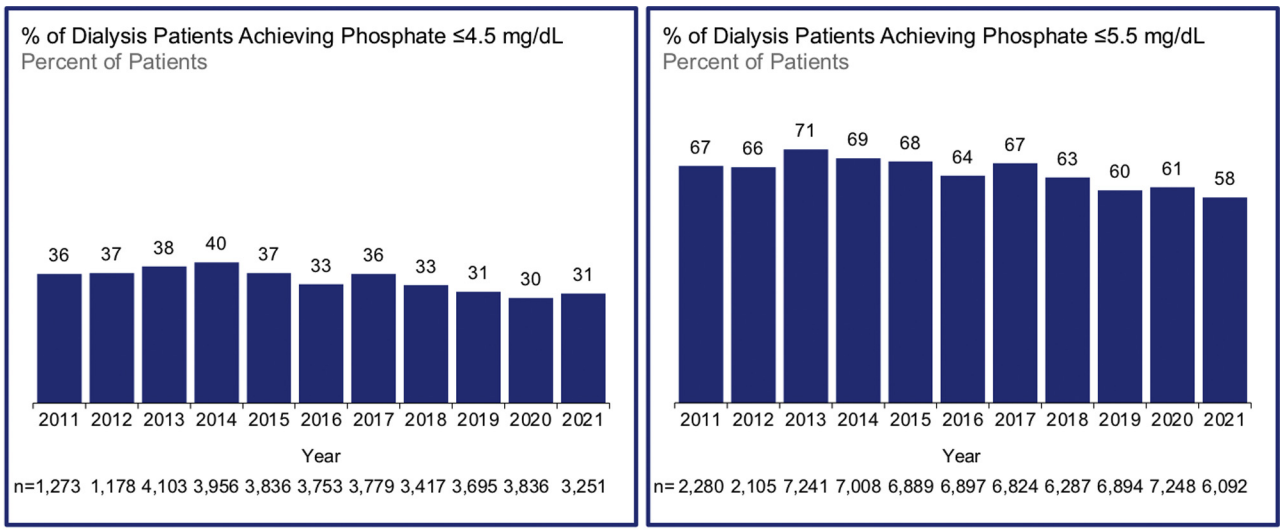

Figure 3. Percent of dialysis patients who achieved target phosphate from 2011 to 2021.[42]

hypothesized to be beneficial (e.g., sevelamer can lower low-density lipoprotein cholesterol but without impact on cardiovascular outcomes),[39] can be detrimental and result in suboptimal efficacy of other drugs and drug-drug interactions.[40] Despite best efforts and currently available approaches (dietary phosphate restriction, dialysis, and phosphate binders), most patients are unable to consistently achieve target serum phosphorus concentrations[9,41] (Fig. 3).

Conclusions and Future of Phosphorus Control in End-Stage Renal Disease

Given the mechanistic understanding of phosphate absorption, new targeted therapeutic innovations, high dietary phosphorus content, and the limitations of the current treatment approach, it is time to consider novel phosphorus management strategies. In the future, one can consider an approach that starts with blocking the paracellular pathway of phosphate absorption. In that case, phosphorus binders become potentially adjunctive, if necessary, in cases of difficult-to-control phosphorus. Phosphate absorption inhibitors are targeted: rather than binding to individual phosphate ions or "soaking up" dietary phosphate, phosphate absorption inhibitors directly block phosphate absorption, reducing phosphate absorption through this targeted mechanism. Paracellular phosphate absorption inhibitors like tenapanor may improve our ability to achieve sustained phosphate control. Tenapanor also likely offers a lower pill burden than phosphate binders and presents an opportunity to target phosphorus control for the study of harder outcomes, particularly bone health. Regulatory changes, such as mandatory labeling of phosphate content (in milligram and percent of daily value) on packaged foods, drugs, and dietary supplements, should also be implemented to help patients curtail dietary phosphorus intake.[43] Identifying kidney-friendly foods using an easily recognized symbol would also be an effective strategy to help reduce phosphorus intake, particularly for patients with poor health or English literacy.[43]

Practical Application

Novel therapies that target gastrointestinal phosphate absorption pathways present an opportunity to rethink hyperphosphatemia management. Clinicians may consider using phosphate absorption inhibitors as a first-line treatment, with adjunctive phosphate binders, if necessary, in hyperphosphatemia.

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