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REVIEW

Hyperphosphatemia in Chronic Kidney Disease: The Search for New Treatment Paradigms and the Role of Tenapanor

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Abstract: Hyperphosphataemia represents a significant challenge in the management of chronic kidney disease, exerting a pronounced influence on the pathogenesis of cardiovascular complications and mineral bone disorders. Traditional approaches to address hyperphosphataemia involve implementing dietary phosphate restrictions, administering phosphate binders, and, in cases of end-stage renal disease, resorting to dialysis. Unfortunately, these interventions frequently prove inadequate in maintaining phosphate levels within recommended ranges. Additionally, commonly employed pharmacological agents are not immune to eliciting adverse events, thereby limiting their prescription and therapeutic adherence. There is a growing focus on exploring novel therapeutic strategies in this context. The current discussion centres on tenapanor, a pharmacological agent predominantly acting as a selective inhibitor of sodium/hydrogen exchanger isoform 3 (NHE3). Its mechanism of action involves modulating tight junctions, resulting in reduced sodium absorption and intestinal paracellular permeability to phosphate. Furthermore, tenapanor downregulates sodium-dependent phosphate 2b transport protein (NaPi2b) expression, thereby impeding active transcellular phosphate transport. Clinical trials have elucidated the efficacy and safety profile of tenapanor. This evidence hints at a potential paradigm shift in the management of hyperphosphataemia. However, the burgeoning optimism surrounding tenapanor warrants tempered enthusiasm, as further research remains indispensable. The imperative lies in meticulously delineating its efficacy and safety contours within the crucible of clinical practice. In this review, we synthesize the intricate interplay between hyperphosphataemia and Chronic Kidney Disease-Mineral Bone Disorder, and we discuss the existing pharmacological interventions for hyperphosphataemia and explore emerging treatment paradigms that offer novel perspectives in managing elevated phosphate levels in CKD patients.

Keywords: Chronic Kidney Disease-Mineral Bone Disorder, CKD-MBD, diet, phosphate binders, phosphate intestinal absorption, tenapanor

Introduction

CKD-MBD (Chronic Kidney Disease-Mineral Bone Disorder) is a bone mineral metabolism alteration secondary to chronic kidney disease (CKD) that, according to the definition provided by the 2006 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, includes one or more of the following signs: abnormal metabolism of calcium, phosphorus, vitamin D or parathyroid hormone (PTH); impaired bone mineralization, volume, turnover, strength, or linear growth; development of calcifications in the vasculature or other soft tissues.[1]

The responsible alterations of bone mineral disorders are established in the initial stages of CKD and are associated with a poor quality of life and a low life expectancy.[2] Abnormalities in calcium-phosphorus metabolism are due to the activation of compensation mechanisms, aimed at controlling calcium and phosphorus homeostasis. These mechanisms are mainly represented by the early increase in phosphaturic hormones, such as fibroblast growth factor 23 (FGF23) and PTH, and by a reduced expression of klotho, the FGF23 co-receptor agonist, which allows its physiological actions on target organs.[3] FGF23 is a phosphatonin produced by osteocytes and has a phosphaturic action. Its production is therefore stimulated by hyperphosphataemia. The increase of FGF23 reduces serum phosphate levels because it regulates the

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proximal tubular reabsorption of phosphorus, through the inhibition of the co-transporter NaPi2a, reduces 1, $25(OH)_2$ vitamin D production by inhibiting the alpha1-hydroxylase enzyme, and decreases PTH synthesis by binding to its receptor present on parathyroid cells. These actions are linked to the interaction with its co-receptor agonist Klotho. Klotho deficiency, which appears to be one of the first alterations found in CKD-MBD, determines resistance to the action of FGF23, which subsequently increases in the circulation due to increased bone production. The consequences are the following: reduced activation of vitamin D and increase in circulating levels of PTH with the onset, as renal failure progresses, of parathyroid glands hyperplasia and secondary hyperparathyroidism; hypocalcaemia, due to reduced intestinal absorption and renal resorption of calcium, and hyperphosphataemia caused by reduced phosphorus renal excretion.[4]

These adaptive mechanisms, which are basically aimed at maintaining a neutral phosphorus balance, transform into maladaptive processes that support hyperphosphataemia and bone reabsorption of calcium when renal function gradually declines. Accordingly, CKD patients progressively develop established skeletal abnormalities, represented by an increased risk of bone lesions due to the onset of renal osteodystrophy (osteitis fibrosa, osteomalacia, adynamic bone disease, osteopenia, osteoporosis),[1] and extraskeletal complications, mainly characterized by an increased cardiovascular risk due to the formation of calcifications of the tunica media of the arterial wall and soft tissues and by left ventricular hypertrophy, which are both predictors of poor prognosis in patients suffering from CKD.[5–7]

Other consequences related to CKD-MBD can be endocrine disorders, disorders of the immune system, behavioural changes, and alterations of erythropoiesis.[4]

Pathophysiology and Effects of Hyperphosphataemia in Chronic Kidney Disease

Hyperphosphataemia is defined by a serum level higher than 4.5 mg/dL or 1.78 mmol/L.[8] In general population the incidence of such alteration is about 12%,[9] whereas it ranges from 50 to 74% in patients with end-stage renal disease.[10] In critically ill patients, a recent meta analysis reported an incidence of elevated serum phosphate levels of approximately 21%.[11]

The most common cause of higher serum phosphate is kidney failure. In particular, phosphate excretion is reduced when glomerular filtration rate falls below 30 mL/min while, during the earlier stages of CKD, the activation of compensatory mechanisms, namely an increase in FGF-23 and PTH expression, prevents the onset of hyperphosphataemia.[12] Less common causes are high intake, for example due to the use of phosphate-containing laxatives or vitamin D intoxication, or increased renal reabsorption, occurring in conditions such as hypoparathyroidism, volume depletion, metabolic alkalosis, chronic hypocalcaemia, acromegaly or thyrotoxicosis. Rarely, genetic causes can lead to hyperphosphatemia. Moreover, hyperphosphatemia can occur in the setting of tumour lysis syndrome because of the massive release from intracellular space.[13] Finally, several drugs may facilitate the onset of hyperphosphataemia as an adverse reaction, including penicillin, steroids, loop diuretics, and thiazides. Hyperphosphataemia must be differentiated by pseudohyperphosphataemia, which is due to an interference in circulating phosphate measurement that may occur in specific conditions including hyperglobulinemia, hyperbilirubinemia or hyperlipidaemia.[14]

Clinically, even if patients are usually asymptomatic, high serum phosphate increases morbidity and mortality especially in dialysis patients. Cardiovascular disease is the leading cause of death among people suffering from end-stage renal disease and hyperphosphataemia is one of the non-traditional CKD-related cardiovascular risk factors, since it favours left ventricular hypertrophy, heart failure, vascular calcification, and arteriosclerosis.[15] In particular, hyperphosphataemia is able to induce a switch from vascular smooth muscle cells to osteoblast-like cells, leading to medial calcification; in coronary arteries this mechanism may enhance vulnerability of atheromatous plaque, whereas in large vessels it can cause increased arterial stiffness and augmented pulse pressure.[16,17] Other proposed mechanisms in medial arterial calcification include promotion of hydroxyapatite crystals precipitation or extracellular matrix remodelling.[18]

A positive association between carotid intima-media thickness and phosphate concentration has been described by Ishimura et al in CKD patients receiving maintenance haemodialysis.[19] Also, Jung et al performed a cross-sectional study including 54 haemodialysis patients in which they found a strong association between phosphate concentration, pre-dialysis blood pressure and markers of endothelial cell dysfunction such as total peripheral resistance and endothelin-1.[20]

Recently, it has also been suggested that excessive phosphorus intake may contribute to statin resistance in haemodialysis patients, due to greater intestinal absorption and increased synthesis of cholesterol.[21,22]

Hyperphosphataemia rises mortality also in non-dialysis dependent CKD patients. A large prospective longitudinal study including 1203 patients found that higher serum phosphate was independently associated with an increased risk for all-cause and cardiovascular death in patients with CKD stages 3 to 4.[23] Similarly, an association of calcium, phosphate and intact PTH serum levels with mortality was observed among patients with stage 4 and 5 CKD in the PECERA study, a prospective open-cohort study evaluating data from 966 subjects.[24] Among kidney transplant recipients acute phosphate nephropathy is a described cause of graft failure.[25]

Hyperphosphataemia plays a role as a risk factor for negative outcomes also in acute patients. A recent meta-analysis from Zheng et al, which included 47,570 critically ill patients from nine studies, concluded that hyperphosphataemia was associated with an increased risk of mortality (OR 2.82).[11] Al Harbi et al reported a link between hyperphosphataemia and increased mortality, vasopressor use and mechanical ventilation dependence in intensive care unit.[26] Recently, Black et al performed a retrospective study in hospitalized septic patients and found that patients in the highest quartile of first 24-hour phosphate levels had increased mortality and odds of death when compared to other patients (Q4 vs Q1 $p < 0.01$, Q4 vs Q2 $p < 0.01$ and Q4 vs Q3 $p = 0.04$).[27] Similarly, Liu et al concluded that in septic patients hyperphosphataemia is an independent mortality risk factor and that the risk of death is higher when phosphate is higher.[28]

High serum phosphate consequences can also involve central nervous system with hyperreflexia, muscle cramping, neuromuscular hyperexcitability or even delirium, coma or tetany. Furthermore, hyperphosphataemia has been observed to increase the risk of haemorrhagic stroke in dialysis patients,[29] the risk of incident dementia[30] and the decline of cognitive functions in pre-dialysis patients.[31]

Currently Available Drugs in the Treatment of Hyperphosphataemia

Since hyperphosphataemia is associated with increased morbidity and all-cause mortality in patients with later stages of CKD,[15] maintaining phosphate homeostasis is mandatory in this high-risk population. To achieve such purpose a multifaceted approach integrating dietary modifications, pharmacological interventions and dialysis is required, the latter being obviously limited to patients with end-stage renal disease.[32] The intricate interplay between these elements is crucial for achieving optimal outcomes in the complex landscape of CKD management.

Dietary interventions serve as a cornerstone in controlling hyperphosphataemia. Patients are not only instructed to limit the intake of phosphorus-rich foods, such as dairy products, certain meats, nuts, seeds, and processed foods with phosphorus additives, but are also educated on advanced cooking techniques like leaching and soaking.[33] The overarching goal is to curtail the total phosphorus burden on the kidneys by mitigating dietary sources.

As CKD progresses, dietary restrictions alone may become insufficient,[34] hence phosphate binders emerge as pivotal components of the therapeutic strategy.[35] These medications operate within the gastrointestinal tract, binding dietary phosphorus and impeding its absorption.[36]

While calcium-based binders like calcium carbonate or calcium acetate are conventionally employed, the choice may shift towards non-calcium-based alternatives, such as sevelamer or lanthanum carbonate, particularly in patients with hypercalcaemia or those at risk for vascular calcification.[34,37] Calcium-based binders, in fact, carry the risk of inducing hypercalcaemia. In addition, prolonged exposure to elevated calcium levels may contribute to vascular and soft tissue calcification, posing concerns for cardiovascular health over the long term. Non-calcium-based binders, although they reduce the risk of hypercalcaemia, are not without their own set of considerations. Gastrointestinal side effects, including nausea, vomiting, and constipation, are frequently reported with their use.[38,39] These symptoms, while generally manageable, can impact patient adherence to therapy and quality of life.

Another class of drugs is represented by aluminium-containing agents, which, though effective, face limitations due to concerns about potential toxicity from aluminium accumulation.[34,39] Chronic exposure to elevated aluminium levels is associated with neurotoxicity, manifesting as cognitive dysfunction, and an increased risk of bone diseases, including osteomalacia.[39,40]

An emerging and promising class of phosphate binders involves iron-based compounds devoid of calcium, namely sucroferric oxyhydroxide and ferric citrate.[35] These binders not only effectively control phosphate levels but also address

concurrent issues of anaemia and iron deficiency frequently encountered in CKD patients.[41] Main potential adverse effects of the iron-based phosphate-lowering agents are discoloured tools and mild and transitory diarrhoea.[35]

The landscape of phosphate binder efficacy is complex and influenced by various factors. Comparative studies have produced diverse results, with some indicating potential benefits of non-calcium-based binders, like lanthanum carbonate, especially concerning coronary artery calcification and cardiovascular outcomes.[42] However, the complexity of these interactions is underscored by conflicting findings, exemplified by studies like LANDMARK.[43,44]

Other studies have shown that sevelamer, beyond its efficacy in managing hyperphosphataemia, has been associated with improved patient outcomes. In particular, a reduced all-cause mortality has been reported in dialysis patients[45] as well as in nondialysis-dependent CKD patients.[46,47]

Moreover, its use is correlated with positive metabolic changes, including lower glycated haemoglobin, improved high-density lipoprotein levels, and reductions in low-density lipoproteins and total cholesterol compared to traditional calcium-based binders.[48]

In dialysis, particularly for patients grappling with persistent hyperphosphataemia, an intriguing consideration is the potential benefits of intensified haemodialysis therapy, notably through prolonged-duration dialysis sessions.[49] This approach seeks to minimize the rebound effect of serum phosphate levels after each dialysis treatment, arising from phosphorus deposits of the body.

In summary, the choice between dietary management, pharmacological intervention, and selecting a specific phosphate binder should be highly individualized. A holistic assessment of the patient's nutritional status, existing comorbidities, and response to treatment is indispensable. Regular monitoring of serum phosphorus levels and other pertinent laboratory parameters is essential for making informed adjustments to the treatment plan, ensuring optimal outcomes in the intricate and evolving landscape of CKD management.

As mentioned above, currently available phosphate binders have limitations related to side effects, such as the risk of hypercalcaemia or aluminium accumulation, along with potential gastrointestinal discomfort. It is also noteworthy that the total number of pills, particularly when choosing binders such as sevelamer, and the amount of phosphorus chelators prescribed are associated with non-adherence. In this context, developing new drugs should aim to overcome these limitations by providing safer and more effective therapeutic options. This may include innovative compounds with specific mechanisms of action that reduce serum phosphorus without negatively affecting calcium, causing fewer gastrointestinal side effects, increasing the patient's adherence, and positively influencing other issues related to CKD.

New Treatment Paradigms in the Management of Hyperphosphataemia in CKD Patients

The current integrated approach to hyperphosphataemia in patients with later stages of CKD shows multiple limitations.

As stated above, a proper nutritional regimen has a pivotal role in the control of hyperphosphataemia. Nevertheless, Kidney Disease Outcomes Quality Initiative guidelines do not suggest a specific optimal range of phosphate intake given that serum phosphate levels are influenced not only by diet, and then intestinal absorption, but also by phosphate exchange between blood and bone and by excretion with the urine in patients still having a residual renal function.[50] Moreover, since phosphorus intake is closely related to protein consumption, an excessively restrictive diet can impair quality of life[51] but especially it may expose CKD patients to the risk of protein malnutrition, with potentially increased mortality.[52]

Another issue worth mentioning is that many additives present in medications and in packaged foods constitute sources of the so-called hidden phosphorus, which is difficult to measure and control. Some drugs containing phosphate are commonly prescribed to CKD patients and include amlodipine, lisinopril, bisoprolol and many others.[53] The inorganic phosphate, which is largely present in processed and preserved foods, is even more efficiently and promptly absorbed (80–100%) in the gastrointestinal tract and subsequently more bioavailable compared to the phosphate derived from organic sources (40–60%), with phosphate of animal origin more completely absorbed than that coming from vegetal foods.[54] As a consequence, a particular attention must be paid also to the type and source of phosphate in addition to the amount of phosphate itself.

Phosphate binders effectively reduce intestinal absorption and then serum levels of phosphate. Though, they may become insufficient if dietary phosphate intake remains high and their use is associated with high pill burden and potential side effects, especially at the gastrointestinal level.[12]

With regard to renal replacement therapy, phosphate removal by extracorporeal dialysis may depend on several factors including dialysis modality, type and surface area of the dialyzer membrane, duration of dialysis session, dry body weight, pre-dialysis phosphataemia, serum PTH value and vitamin D supplementation, even though some data from different studies in this regard are controversial.[55] Haemodialysis efficiently removes phosphate excess but diet and phosphate binders are needed in the majority of treated patients to prevent phosphate accumulation in the interdialytic interval. Patients receiving peritoneal dialysis frequently develop hyperphosphataemia because phosphate behaves as a middle-size molecule notwithstanding its low molecular weight. This implies that phosphate transport through peritoneal membrane is noticeably influenced by patient transporter features and dialysis modality and prescription and that phosphate binders and a proper diet are essential to improve serum phosphate control also in this population.[56]

The aforementioned considerations are supported by recent observational data showing that, despite a strict dietary regimen and the use of phosphate-lowering medications, many CKD patients, especially on dialysis therapy, fail to adequately control serum phosphate levels.[57] Accordingly, there is a need for novel pharmacological approaches enabling to better handle hyperphosphataemia and ameliorate clinical outcomes of CKD patients.

The understanding of how phosphate is absorbed in the gastrointestinal tract has suggested an alternative strategy to phosphate binders for reducing systemic absorption of dietary phosphate load. Phosphate absorption occurs through two different mechanisms (Figure 1). Active transcellular transport is mediated by specific transporters such as the sodium-dependent phosphate 2b transport protein (NaPi2b), whose expression is regulated by serum phosphorus values through modifications in activated vitamin D3 levels, or type-III inorganic phosphate (Pi) transporters PiT-1 and PiT-2.[58,59] Conversely, passive paracellular transport occurs through tight junction complexes along the concentration gradient and involves the sodium/hydrogen exchanger isoform 3 (NHE3). This isoform is largely expressed at the gastrointestinal level where it transports sodium ions into cells in exchange for hydrogen ions, in this way playing a crucial role in maintaining water and acid-base balance homeostasis. As a consequence, NHE3 inhibition determines sodium and water

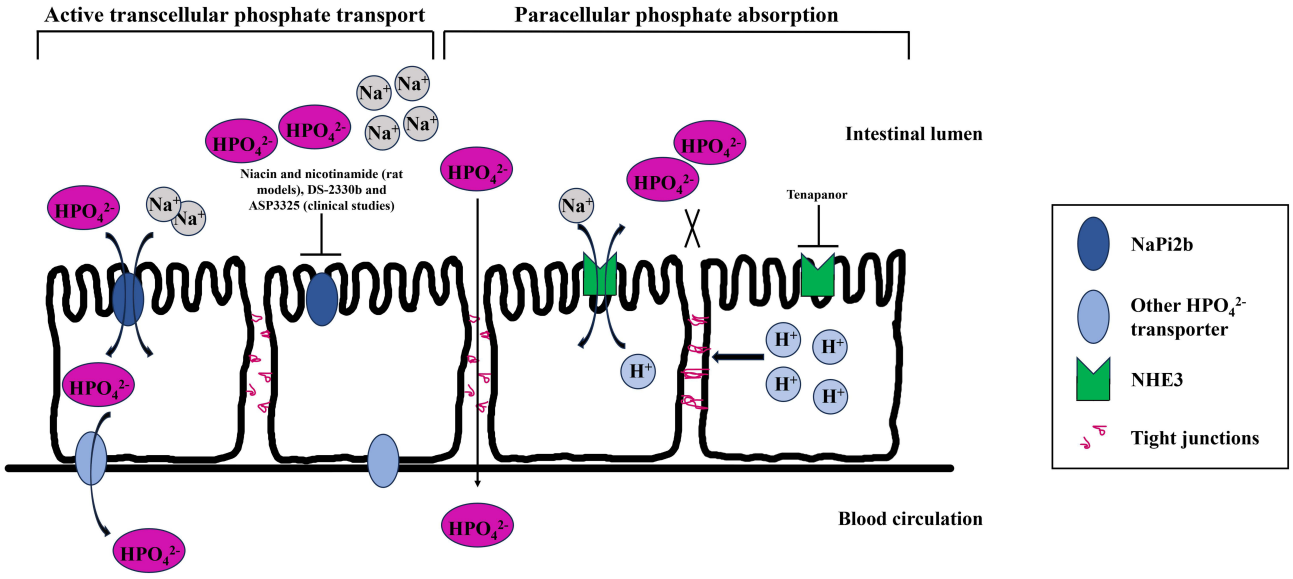

Figure 1 Schematic representation of intestinal phosphate transport.

Notes: Phosphate is absorbed through two different mechanisms in the gastrointestinal tract. Active transcellular transport involves specific transporters such as the sodium-dependent phosphate 2b transport protein (NaPi2b), which can be inhibited by some molecules currently under evaluation for hyperphosphataemia management (Niacin and Nicotinamide in rat models, DS-2330b and ASP3325 in clinical studies). Passive paracellular phosphate transport happens through tight junction complexes along the concentration gradient and involves the sodium/hydrogen exchanger isoform 3 (NHE3), which transports sodium ions into cells in exchange for hydrogen ions; it has been reported that NHE3 inhibition by Tenapanor induces not only a sodium and water retention in the lumen but also an intracellular proton retention with following pH-related conformational change in specific tight junction proteins called claudins and reduction in the transepithelial permeability to phosphate.

retention in the lumen with following decrease in both sodium absorption and blood pressure values. It has been observed that the limited intracellular proton retention induced by NHE3 inhibitors leads to a pH-related conformational change in specific tight junction proteins, named claudins, with resulting reduction in the transepithelial permeability to phosphate and then decrease in phosphate absorption.[59,60]

Based on these mechanisms, growing evidence is accruing on promising pharmacological agents able to interfere with phosphate absorption, targeting one of the two described pathways rather than bind dietary phosphate in the gastrointestinal tract.

Active Transcellular Phosphate Transport Inhibition

Few studies have explored the potential role of active transcellular phosphate transport inhibition on hyperphosphataemia control in CKD patients and the obtained results are uncertain.

Safety and efficacy of the oral NaPi-2b inhibitor DS-2330b have been evaluated in haemodialysis patients in a 2-part randomized, placebo- and active-controlled, Phase 1b trial enrolling six patients in part A (focused on safety and pharmacokinetics of tablet and solution formulations) and 32 patients in part B (assessing safety of solution formulation and its effect on phosphataemia). The Authors concluded that DS-2330b was safe and well tolerated when administered both as a monotherapy or in combination with sevelamer but its efficacy did not show to be clinically significant.[61] Similar results had been previously obtained using the NaPi-2b inhibitor ASP3325 in 124 healthy subjects and in 22 patients with end-stage renal disease receiving haemodialysis. Also in this study, the drug was safe and well tolerated but serum phosphate did not decrease significantly.[62]

Other potential inhibitors of NaPi-2b include niacin and nicotinamide, which have been demonstrated to down-regulate intestinal NaPi-2b expression in rat models.[63–65] Nevertheless, these compounds did not prove to have a significant phosphate-lowering action nor they were able to influence serum markers of mineral metabolism in clinical studies involving CKD patients.[66,67]

More promising results seem to come from using EOS789, a molecule defined as a pan-Pi transporter inhibitor since it is able to inhibit not only NaPi-2b but also PiT-1 and PiT-2 transporters. Safety and efficacy of EOS789 were investigated in a small phase 1b study conducted on haemodialysis patients. The drug was not associated with serious adverse events and a pre-scheduled secondary analysis showed that the higher dose tested significantly reduced intestinal phosphate absorption compared to placebo.[68] Undoubtedly, further and larger studies are needed to confirm these findings.

Paracellular Phosphate Absorption Inhibition

Paracellular absorption pathway seems to be prevalent compared to active transcellular transport as it accounts for about two-thirds of intestinal phosphate absorption. Accordingly, its inhibition may potentially assume greater importance,[69] as demonstrated by the results of clinical trials evaluating the effects of the pharmacological agent tenapanor on serum phosphate. Tenapanor primarily acts as a selective NHE3 inhibitor able to modulate tight junctions with resulting reduction in sodium absorption as well as in the intestinal paracellular permeability to phosphate. Moreover, it decreases NaPi2b expression thereby interfering also with active transcellular phosphate transport.[70]

The effects of tenapanor have been investigated in many trials.

The first studies on humans were conducted on healthy volunteers and demonstrated the safety, tolerability and effectiveness of Tenapanor[71] with probably no influence on intestinal uptake of other drugs, as demonstrated by Johansson et al in 28 healthy subjects. This phase 1 study was designed to assess the potential impact of NHE3 inhibition by tenapanor on the activity of PepT1, a H+-coupled peptide transporter highly expressed in the gut and involved in the transport of dipeptides and tripeptides deriving from protein digestion as well as of several hydrophilic oral drugs. The Authors found that tenapanor administration did not affect the activity of this transporter, suggesting the absence of relevant drug–drug interactions.[72] No pharmacodynamic effects were also reported in healthy volunteers receiving both tenapanor and sevelamer carbonate.[73] Moreover, tenapanor seems to have no influence on CYP3A4 and may therefore be administered in association with drugs metabolized by this cytochrome.[74]

With these assumptions, safety and efficacy of tenapanor were then investigated in haemodialysis patients (Table 1).

Table 1 Clinical Trials Evaluating the Effects of Tenapanor in Haemodialysis Patients

Ref.	Study Design	Population	Active Treatment	Control	Follow-Up Duration	Main Results
75	Phase 2 multicentre randomized, double-blind, placebo-controlled study	162 HD pts with hyperphosphataemia (of whom 115 completed the study)	Six tenapanor regimens (3 or 30 mg once daily or 1, 3, 10, or 30 mg twice daily)	Placebo	4 wks	• Dose-dependent reduction in serum phosphate • Most common adverse event in the active group: diarrhoea
77	Phase 2, double-blind, parallel-group, dose-finding study	207 HD patients with hyperphosphataemia	4 groups (Tenapanor 5 mg twice daily, 10 mg twice daily, 30 mg twice daily or 30 mg twice daily dose-titration)	Placebo	6 wks	• Dose-responsive serum phosphate-lowering action • Most common drug-related adverse event: diarrhoea, mostly mild and tolerable
78	Phase 3 randomized, double-blind trial	219 randomized HD pts with hyperphosphataemia (of which 152 completed both study phases)	1. Twice-daily oral tenapanor (3, 10, or 30 mg for 8 wks) 2. Rerandomization of pts to previously assigned dose or placebo for a 4-wk withdrawal period	Placebo	8 wks + 4 wks	• Significant reduction in mean serum phosphate (decrease of 1.00, 1.02, and 1.19 mg/dl in the three dose groups) • Mean increase of 0.85 mg/dl in the placebo group vs a mean increase of 0.02 mg/dl in the pooled active group • Adverse events: softened stool, slight increase in bowel movement frequency
79	Phase 3 double-blind trial	236 HD pts with hyperphosphatemia already treated with phosphate binders (of which 235 included in the full analysis and 228 completed treatment period)	Twice-daily oral tenapanor 30 mg plus phosphate binder	Placebo plus phosphate binder	4 wks	• Greater mean change in serum phosphorus levels in the tenapanor plus binder group compared to placebo plus binder group (−0.84 vs -0.19 mg/dl, $P < 0.001$) • Most common adverse events in the active group: diarrhoea, nausea
80	Double-blind, multicentre, randomized trial	47 HD pts with hyperphosphataemia not responding to phosphate binders	Twice-daily tenapanor 30 mg plus phosphate binder	Placebo plus phosphate binder	6 wks	• Decrease in mean serum phosphorus from 6.77 mg/dL to 4.67 mg/dL in the tenapanor group and from 7.01 mg/dL to 6.69 mg/dL in the placebo group • Most common adverse event: diarrhoea (65.2% and 8.3% of pts in the tenapanor and placebo groups, respectively)
81	Multicentre, phase 3 trial	564 HD pts with hyperphosphataemia and 1.5 mg/dl phosphate increase after phosphate binder washout	Twice daily tenapanor 30 mg for 26 wks, then rerandomization to tenapanor or placebo for 12 weeks and eligibility for the 14-wk safety extension period	Sevelamer carbonate	52 wks comprising three periods: - a 26-wk open-label randomized therapy period - a 12-wk double-blind placebo-controlled randomized withdrawal period - a 14-wk open-label safety extension period	• Statistically significant difference in estimated mean change in serum phosphate level between tenapanor and placebo (−1.4 mg/dl, $P < 0.0001$) • Most frequent adverse event in tenapanor group: loose stools; serious adverse events more common in the sevelamer carbonate group

Abbreviations: HD, haemodialysis; pts, patients; wks, weeks.

Block et al performed a Phase 2 double-blind randomized trial recruiting 162 haemodialysis patients with hyperphosphataemia and reported a dose-dependent reduction in serum phosphate levels from baseline compared to placebo and a higher frequency of diarrhoea in patients receiving tenapanor.[75] A secondary analysis of this trial has suggested that tenapanor has the ability to decrease FGF23 serum levels in parallel with serum phosphate compared to placebo.[76] The dose-responsive phosphate-lowering effect of tenapanor has also been analysed by Inaba et al in a multicentre phase 2 double-blind dose-finding study where 207 HD patients with hyperphosphataemia were randomly assigned to five

groups: placebo or tenapanor 5 mg twice daily, 10 mg twice daily, 30 mg twice daily, and 30 mg twice daily dose-titration. After 6 weeks, the mean change in serum phosphate was greater as the dose increased. The more frequent drug-related adverse event was diarrhoea.[77]

A Phase 3 double-blind trial evaluated the effects of tenapanor in two phases. First, 219 patients were randomized to receive different doses of twice-daily oral tenapanor (3, 10, or 30 mg) for 8 weeks. Afterward, patients were randomized again to previously assigned drug dose or placebo for 4 weeks. Of patients recruited, 152 completed both phases. The Authors observed a significant decrease in mean serum phosphate in all the treatment groups and tenapanor was demonstrated to be significantly effective compared to placebo in the second study phase. Adverse events were primarily due to the mechanism of action of the drug and were mostly represented by a limited increase in bowel movement frequency and loose stools.[78]

The AMPLIFY Trial analysed the safety and effectiveness of adding tenapanor to phosphate-binder therapy in 236 patients on maintenance dialysis with hyperphosphataemia already treated with phosphate binders. The tenapanor plus binder group showed a greater mean change in serum phosphate compared to the placebo plus binder group after 4 weeks of treatment. The most common adverse event primarily experienced by patients of the active group was a transient mild-to-moderate diarrhoea, followed by nausea.[79] Similar findings were reported by Shigematsu et al in a double-blind, multicentre, randomized, placebo-controlled trial on 47 Japanese haemodialysis patients with hyperphosphataemia not responding to phosphate-binder therapy. Adding tenapanor to phosphate binders induced a greater reduction of serum phosphate concentrations compared to the placebo plus binder group, with diarrhoea being the most usual adverse event also in this study.[80]

The long-term impact of tenapanor was analysed in the PHREEDOM study, a randomized phase 3 trial comparing tenapanor and sevelamer carbonate in 564 maintenance haemodialysis patients with hyperphosphataemia and a 1.5 mg/dl increase in serum phosphate levels after phosphate binder washout. The Authors demonstrated the ability of tenapanor to significantly control hyperphosphataemia with a reasonable safety profile and tolerability.[81]

Lastly, a recent meta-analysis (five randomized clinical trials published up to 1 August 2022 for a total of 533 patients included) by Luo et al confirmed the ability of tenapanor to effectively reduce serum phosphate levels compared to placebo in patients receiving haemodialysis, with common side effects mainly represented by diarrhoea and other gastrointestinal adverse events.[82]

Conclusions

Growing evidence is accruing on the ability of tenapanor to reduce intestinal phosphate absorption both as a monotherapy and when combined with phosphate binders. The use of this drug could allow to overcome the limits of current therapeutic strategies in terms of effectiveness, pill burden, patients' adherence and side effects. Nevertheless, new randomized clinical trials with larger sample sizes and adequate follow-up duration are needed to evaluate efficacy and safety of tenapanor in the long term and introduce this compound in clinical practice for the management of CKD patients with hyperphosphataemia.

Disclosure

The authors report no conflicts of interest in this work.

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