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Review Article

Tenapanor-A Novel Approach for Management of Hyperphosphatemia in End Stage Renal Disease: A Clinical Study Aggregate Review

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Abstract

The critical importance of phosphate regulation in chronic kidney disease (CKD) has been well understood for decades. But new findings, frequently applicable to routine medical care, continue to evolve. Poor health outcomes, greater morbidity, lowered quality of life, and a higher death rate from cardiovascular disease are all linked to the development of CKD-bone mineral ailment. Increased blood phosphate levels are linked to an increased risk of mortality in hemodialysis patients due to changes in phosphate breakdown and declining renal function as CKD advances.In this setting, according to CKD-mineral bone disease recommendations, it is critical to regulate serum phosphate levels in patients with CKD-mineral bone problem. If dialysis and dietary intervention fail to control blood phosphate levels, the use of phosphate binders is advised. Although phosphate binders are successful in lowering blood phosphate levels by actively binding to dietary phosphate, certain individuals have adverse effects that may restrict their use.These medications also have a significant pill load, which might result in poor treatment compliance. Tenapanor, a novel medication, works by inhibiting the sodium/hydrogen exporter isoform 3 (NHE3), which lowers intestinal phosphate absorption primarily by decreasing passive paracellular phosphate flow. Tenapanor also reduces the expression of the sodium phosphorus 2b transport protein (NaPi2b), which limits active transcellular phosphate absorption compensation. This is considered to be more effective phosphorous absorption regulator and a better target for tailored medication therapy. This clinical study aggregate report explores the currently published studies that have evaluated Tenapanor for the treatment of hyperphosphatemia in end stage renal disease patients on haemodialysis.

Keywords: Tenapanor, phosphate binding agents, hyperphosphatemia, chronic kidney disease, phosphate control, phosphate binders, phosphate absorption, phosphate absorbtion inhibitor.

INTRODUCTION

Chronic kidney disease has multifaceted impacts on our bodies, affecting both physiological and biological mechanisms. It disrupts fluid and electrolyte balance, pH regulation, blood pressure regulation, vitamin D metabolism, and the excretion of toxins and waste materials [1]. Advanced chronic kidney disease often leads to hyperphosphatemia due to imbalances in phosphate homeostasis, resulting in vascular calcification, left ventricular hypertrophy, arterial stiffness, increased cardiovascular risk, and mortality [2-4]. The primary strategy to address hyperphosphatemia involves modifying dietary phosphate intake, but this can be complicated by the need for essential dietary protein. Achieving the right balance of phosphate in chronic kidney disease management remains crucial, as protein and phosphate control may exacerbate the patient's condition[5] . As chronic kidney disease progresses, bone and mineral metabolism become dysregulated, with elevated parathyroid hormone levels attempting to maintain normal phosphorus and calcium levels. However, in end-stage renal disease, this response may become nonadaptive, leading to exponentially increased phosphate levels [6]. The KDIGO 2017 Clinical Practice Guideline Update for Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) recommends various strategies to prevent hyperphosphatemia, including dietary restrictions, phosphate binding therapy, and intensive dialysis for end-stage renal disease patients. However, the effectiveness of these approaches in lowering serum phosphate levels is not consistent [7]. Given this inconsistency, it is essential to explore ways to enhance the effectiveness of dietary phosphate restriction, especially the use of phosphate binders, in patients with end-stage renal disease. Poor adherence to phosphate binder therapy is often attributed to factors like large pill size and patient ignorance about their condition and treatment [8]. Phosphate binders function by forming insoluble compounds with dietary phosphate, which are then eliminated through the digestive system. However, their limited binding capacity necessitates numerous tablets, which are insufficient to control daily dietary phosphate intake and may result in potential drug interactions [9-13]. As a result, many stage 5 renal disease patients struggle to maintain normal serum phosphorus levels. New targets have been identified to inhibit intestinal phosphorus transport, potentially offering more effective control of phosphorus compared to conventional phosphate binding therapies [14]. Recent research highlights the paracellular phosphate pathway as the primary mechanism for intestinal phosphate absorption, which should be considered in new phosphate management systems [15]. Tenapanor, a NHE3 inhibitor, has shown promise in reducing serum phosphate concentrations and presents a cutting-edge approach to treating CKD-MBD [17-19]. Tenapanor primarily inhibits passive paracellular phosphate transport and reduces the expression of NaPi2b, providing a novel method to manage hyperphosphatemia [20].

METHODS

Using the search engines PubMed, KDIGO guidelines, NIH library - a review of the literature was done to finish this narrative review. For the above search engines, the keyword "tenapanor hyperphosphatemia" was entered. Results were restricted to studies that were written in the English language, and review articles were not included. Studies on humans, animals, and in vitro were all included. There was no time frame mentioned.

DISCUSSION

Tenapanor, a minimally absorbed small molecular inhibitor of gastrointestinal sodium-hydrogen exchanger isoform 3, has undergone phase 3 clinical trials for the treatment of irritable bowel syndrome along with constipation [21]. Furthermore, tenapanor exhibits its action by inhibiting passive paracellular phosphate mobilization in the gastrointestinal tract, leading to a reduction in serum phosphorus levels from baseline. This mechanism of action contributes to the management of hyperphosphatemia in patients with end-stage renal disease [22]. Animal studies suggest that tenapanor exerts its effects primarily in the gut region, with minimal systemic absorption. The majority of the drug is excreted unchanged in the urine [23] ·In vitro clinical trials were conducted to evaluate potential drug interactions, specifically assessing its impact on the cytochrome P450 (CYP) class of enzymes. The results indicate that tenapanor has a significant effect on five out of the seven cytochrome enzymes, particularly CYP3A4/5, while it does not inhibit CYP1A2. Notably, there were no observable drug-drug interactions with drugs metabolized by CYP3A4 enzymes, allowing for potential coadministration [24]. Due to its limited systemic bioavailability, tenapanor has minimal exposure to other drugs, resulting in negligible potential for drug-drug interactions and supporting the absence of requirements for dose adjustments [25] . In a prospective observational clinical trial, tenapanor in combination with phosphate binders (sevelamer) demonstrated a more substantial reduction in serum phosphate levels compared to monotherapy with phosphate binders alone [26] · This lack of drug-drug interaction between phosphate binding agents and tenapanor is significant, as dual treatment with these medications may be necessary for individuals with chronic hyperphosphatemia. Current treatments with phosphate binders in hemodialysis patients have shown varying levels of efficacy in reducing serum phosphate levels, as suggested by clinical practice guidelines. Tenapanor exhibited lower increases in serum phosphate levels compared to the placebo group, although it was not sufficient to meet all clinical practice guideline targets [27]. One notable limitation of tenapanor is the occurrence of severe adverse events, particularly diarrhea, reported during clinical trials [28].An associated concern with the use of phosphate binders is patient non-adherence, with reported rates ranging from 22% to 74%. Phosphate binders require administration with meals, often necessitating high daily doses of up to 8-9.6 grams per day, leading to a significant pill size burden [29]. Tenapanor, administered in milligram quantities once or twice daily, significantly reduces the pill burden, potentially improving patient compliance with the therapy[30]. The ongoing trial, known as NORMALIZE (NCT03988920), is currently investigating the clinical significance of tenapanor. Its primary objective is to assess the proportion of patients achieving a normal serum phosphorus concentration (2.5-5.5 mg/dL) [31]. Within the realm of clinical studies, only one, AMPLIFY, has ventured into examining the combination of tenapanor with phosphate binder therapies. In this study, various phosphate binders were tested, including sevelamer and non-sevelamer binders. Interestingly, the specific binders comprising the non-sevelamer group were not disclosed. However, the outcome revealed that Tenapanor + binder led to a significantly greater reduction in serum phosphorus compared to placebo + binder (-0.84 vs. -0.19 mg/dL; $P < 0.001$) . Notably, the study did not incorporate a tenapanor monotherapy group, preventing a definitive statement about the additive or synergistic effects of tenapanor. Nevertheless, given the complementary mechanisms of action, some degree of synergy is likely[26] . It is worth noting that all clinical trials involving human subjects so far have been conducted in end-stage kidney disease (ESKD) patients undergoing maintenance hemodialysis. These trials have provided evidence that tenapanor, whether used alone or concurrently with phosphate binders, effectively lowers serum phosphorus levels. This suggests that hemodialysis patients currently taking phosphate binders to manage uncontrolled hyperphosphatemia may find relief in tenapanor, potentially reducing their overall pill burden. Interestingly, adherence to phosphate binders has been observed to be low at 38%, with phosphate binders accounting for half of a patient's total pill regimen [28]. In terms of dosing, tenapanor has been administered at doses ranging from 10-30 mg twice daily, without regard to meals, in the studies presented here. This dosing schedule, combined with the pill burden, could be significantly lighter compared to phosphate binders, which typically require administration three times daily with meals. Consequently, the twice-daily dosing of this drug could prove beneficial for patients struggling with excessive pill loads. Lastly, although not specifically studied in humans, tenapanor is not expected to induce cardiovascular calcification, as it lacks calcium—a distinction from other calcium-containing phosphate binders like calcium carbonate. Based on the evidence presented, it appears that tenapanor, when used in conjunction with phosphate binders, offers the most substantial reduction in serum phosphorus concentrations [26]. The Food and Drug Administration (FDA) informed the medication manufacturer Ardelyx, the manufacturer of tenapanor, in a Complete Response Letter in July 2021 that additional important clinical data were required before approval for the diagnosis of hyperphosphatemia could be given. Although the latest information definitely demonstrates a decrease in serum phosphorus concentrations, further research is necessary to determine the size of this effect [32].

SUMMARY OF IN VITRO, ANIMAL AND HUMAN STUDIES FOR TENAPANOR

1. HUMAN STUDIES

AUTHOR	STUDY DESIGN AND OBJECTIVE	NUMBER OF PATIENTS	TREATMENT AND DRUG	OUTCOMES
Pablo E Pergola , David P Rosenbaum , Yang Yang , Glenn M Chertow [26]	**Randomised Control Trial** – Human Study To evaluate the efficacy of phosphate binders , and the Tenapanor in treatment of hyperphosphatemia in patients with maintainance dialysis	Out of 511 , the 236 were randomised patients 116 in tenapanor plus binder group ,and 119 in placebo plus binder group	Participants received tenapanor 30 mg twice daily , and also placebo The above regimen was followed for 4 weeks .	A dual therapy with phosphate binders , and tenapanor had a greater efficacy in reducing the phosphorus levels to the baseline than the phosphate binders therapy alone .
Takashi Shigematsu , Yotaro Une , Kazuaki Ikejiri , Hironori Kanda , Masafumi Fukagawa , Tadao Akizawa [22]	Double-blind, randomized, placebo-controlled trial. human study To compare the efficacy between add on tenapanor and phosphate binders monontherapy in patients with refractory hyperphosphatemia	N = 47 Patients with refractory hyperphosphatemia Randomly assigned to tenapanor and placebo group	Participants received tenapanor and placebo for a period of 6 weeks . Tenapanor –30mg daily - PO – twice daily before the meal	Particpants treated with tenapanor add on therapy achieved serum phosphorus target level at a faster rate compared to that of placebo .
Block GA, Bleyer AJ, Silva AL, Weiner DE, Lynn RI, Yang Y, Rosenbaum DP, Chertow GM. [27]	Randomised phase 3 trial carried out for 52 weeks -- human study To evaluate the safety and efficacy of tenapanor in controlling target serum phosphorus levels in patients with maintainance dialysis	Maintainance dialysis , N = 564 Patients were randomly assigned to , Tenapanor , N =423 And phosphate binders,Sevalamer ,N =141	Tenapanor was titrated in 10 mg increments , with a minimum dose of 10 mg twice daily , gradually exceeding to a maximum dose of 30 mg twice daily.Patients were randomized to receive tenapanor for 26 weeks , and sevalamer for 52 weeks .Patients who received tenapanor , were rerandomized again to continue tenapanor for 12 weeks , and placebo for 12 weeks .	Results showed reduction in mean serum phosphorus levels with tenapanor therapy .
Block Ga, Rosenbaum Dp, Leonsson-Zachrisson M, Åstrand M, Johansson S, Knutsson M, Langkilde Am, Chertow Gm.. [29]	Randomised , double blind , placebo controlled multicenter study . This study was done to determine the consequence of tenapanor therapy in maintaining the serum phosphorus levels within the patients who receieved haemodialysis.	597 patients were screened , 162 patients were randomized to determine the dose dependent reduction in serum phosphorus levels .	Patients were randomly assigned to receive any one of the tenapanor doses , 3 or 30 mg once daily and 1,3,10, 30 mg twice daily .	Tenapanor once or twice daily regimen had significant impact in reducing the serum phosphorus levels in patients with haemodialysis .

IN VITRO AND ANIMAL STUDIES

AUTHOR	STUDY DESIGN AND OBJECTIVE	NUMBER OF PATIENTS	TREATMENT AND DRUG	OUTCOMES
Johansson S, Leonsson-Zachrisson M, Knutsson M, Spencer AG, Labonté ED, Deshpande D, Kohler J, Kozuka K, Charmot D, Rosenbaum DP. [33]	INVITRO STUDY Open label two way cross over study Obj - To evaluate Drug drug binding study inorder to determine the systemic exposure when the drugs are coadministered .	-----	Tenapanor tritrated to final conceneteration of 1, 10, 50, 100, and 200 µM + Sevalamer concenteration of 1.6mg/ml , calcium acetate 1mg/ml , and calcium carbonate 2.4 mg/ml	Experimental data showed interaction between the sevalamer and tenapanor , the results claimed 72%–87%, tenapanor being bound . No interaction was found between calcium acetate, calcium carbonate and tenapanor when coadministered
Johansson S, Leonsson-Zachrisson M, Knutsson M, [33]	ANIMAL STUDY Obj – To evaluate the invivo drug drug binding pharmacodynamic effects between tenapanor and the phosphate binders .	Sample size – 60 Seven-week-old male Sprague-Dawley rats	Tenapanor was titrated to concenteration of 0.1, 0.3, 1, or 3 mg/kg by dissolving with water . Sevalamer carbonate - 48mg/kg	There was no considerable change in effects produced pharmacodynamically when tenapanor was coadministered with sevalamer . Administering tenapanor 10 mins after administration of sevalamer also showed undetected changes in pharmacodynamics.
King AJ, Kohler J, Fung C [34]	ANIMAL STUDY Objective - to evaluate the effect of tenapanor on rats phosphate excretion in their urine	Sample size – 102 8 week old male Sprague dawley rats	Tenapanor given with 0.15 mg /kg BID along with sevelamer 0.75%to 3%	Administration of the drugs tenapanor and the sevelamer resulted in a more profound decrease in urinary phosphorous levels
King AJ, Siegel M, He Y [35]	ANIMAL STUDY Obj – to find out the mechanism by which the tenapanor results in decrease of gastrointestinal phosphate uptake	Sample size - 5 to 7 healthy rats in each group for all experiments	Different tenapanor doses based on the experiment done .	Tenapanor works by modulating tight junctions, which raise transepithelial electrical resistance and lower phosphate permeability, which inhibits paracellular phosphate absorption. By lowering NaPi2b expression, tenapanor hinders active transcellular phosphate transport.
Johansson et al ,2017. [36]	INVITRO STUDY Objective - Analyze the pharmacodynamic effects simultaneous administration of tenapanor with phosphate binders	Sample size N/A	Tenapanor – 1 , 10 ,50 ,100 and 200 µM + Sevelamer carbonate 1.6mg/ml and calcium carbonate 2.4mg /dL	Tenapanor was shown to be bound in amounts ranging from 72 to 87%, pointing to a possible interaction with sevelamer carbonate. Tenapanor did not bind to either calcium carbonate or calcium acetate.

CONCLUSION

Tenapanor is an experimental new phosphate absorption inhibitor that works on the major phosphate absorption pathway to treat hyperphosphatemia in an alternative approach. Tenapanor has demonstrated an unique mechanism of action that reduces paracellular absorption of phosphate in the gastrointestinal tract by local inhibition of the NHE3, leading to reduced sodium absorption and proposed conformational changes in claudin proteins present in tight junctions that directly decrease the permeability of the paracellular pathway to phosphate. In contrast to phosphate binders, when used as standalone therapy, this may lessen the excessive pill load. Tenapanor can be used without attention to meals and no clinically relevant interactions between medications have been found. The only negative effects were

those brought on by its recognized mechanism of action, which raises the salt and water content of the stool. Tenapanor can therefore be a straightforward but effective hyperphosphatemia therapy with a unique mode of action distinct from standard phosphate binders, with manageable safety profiles, and reduced pill load, which is necessary for patients with CKD and hyperphosphatemia who are on hemodialysis. Further significant, randomized studies on utilization of tenapanor in patients with CKD and ESKD that are optimized for cardiovascular outcomes are required, especially for distinct populations who have not been sufficiently represented in prior studies.

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AUTHOR CONTRIBUTIONS

N.K and L.L conceived and designed this systematic review. N.K, L.L and M.S performed the literature search. N.K and L.L analyzed the data and drafted the content accordingly. M. S. edited and revised the drafted content. Then all the three approved the final version of the drafted review.

COMPETING INTERESTS

The authors declare no competing interests.

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