Tenapanor: A New Treatment Option for Hyperphosphatemia in End Stage Kidney Disease

Tiffany Lin¹, Akram Al-Makki², Brian Shepler¹

¹Department of Pharmacy Practice, Purdue University College of Pharmacy, West Lafayette, IN, USA; ²IU Health Arnett Nephrology, Lafayette, IN, USA

Corresponding author: Brian Shepler, PharmD., Purdue University College of Pharmacy, 575 Stadium Mall Drive, West Lafayette, IN 47907-2091, United States; TEL: (765)-494-1365; email: sheplerb@purdue.edu

Received, September 24, 2021; Revised, January 13, 2022; Accepted January 14, 2022; Published, January 18, 2022

ABSTRACT -- Purpose: This narrative review explores the currently published studies that have evaluated tenapanor for the treatment of hyperphosphatemia in end-stage kidney disease (ESKD) patients on hemodialysis. This medication’s new phosphate lowering mechanism of action reduces intestinal phosphate absorption predominantly through reduction of passive paracellular phosphate flux by inhibition of the sodium/hydrogen exporter isoform 3 (NHE3). Tenapanor additionally prevents active transcellular phosphate absorption compensation by decreasing the expression of sodium phosphorus 2b transport protein (NaPi2b). Methods: A comprehensive search of the literature was conducted using PubMed and ClinicalTrials.gov search engines. The search term “tenapanor hyperphosphatemia” was used for study retrieval. Results were limited to studies published in the English language and excluded review articles. Human, animal, and in vitro studies were included. No date range was specified. Results: A total of 11 primary studies were identified and included in this review, the largest human study of which enrolled 236 patients. Each study is presented in table format along with measured end points. Conclusions: Tenapanor is the first drug in its class that lowers hyperphosphatemia in ESKD patients through a novel mechanism of action involving paracellular inactive transport. Although more studies are needed, early results indicate that tenapanor may have a place in managing hyperphosphatemia in ESKD patients both as monotherapy and as an adjunct to existing phosphate binder therapy.

INTRODUCTION

Hyperphosphatemia is a significant complication that plagues nearly all patients with late-stage chronic kidney disease (CKD) and end-stage kidney disease (ESKD) (1). This is a consequence of the deteriorating kidney’s inability to excrete phosphorus from the body thereby allowing dietary phosphorus absorption and serum accumulation. Hyperphosphatemia in ESKD can lead to secondary hyperparathyroidism, renal osteodystrophy, metastatic calcification, and cardiovascular mortality. In addition to dietary restriction of phosphorus and hemodialysis, drugs that bind phosphate in the gut are usually needed as well (2). The Kidney Disease Improving Global Outcomes’ (KDIGO) latest hyperphosphatemia guidelines recommend treating hyperphosphatemia by limiting phosphorus intake from the diet and using phosphate-binding medications (1). Phosphate binders continue to be a mainstay of treatment for hyperphosphatemia and exist in several different categories including the oldest calcium-containing binders (calcium carbonate, calcium acetate), the polymer-based binder (sevelamer carbonate), the metal-based binders (lanthanum carbonate, aluminum hydroxide) and the newest additions to the armamentarium, the iron-based binders (sucroferric oxyhydroxide, ferric citrate) (3). These medications all control phosphorus absorption by binding to dietary phosphorus in the gastrointestinal tract and allowing the chelate to pass from the body into the feces. Aluminum hydroxide is no longer recommended for long-term use because of concerns about its toxicity, and calcium citrate should be avoided in all CKD patients since citrate can markedly increase intestinal aluminum absorption (4,5).

Recent developments in the understanding of how phosphorus is absorbed from a mechanistic standpoint have allowed innovative new therapies to be conceptualized. From animal model studies, two distinct mechanisms for phosphorus absorption have been identified. Active transcellular transport
through specific ion transporters and inactive paracellular transport which occurs through tight junctions of cells in the duodenum are new biologic pathways for phosphorus absorption from the gastrointestinal tract (6). Active transcellular transport is facilitated through the sodium phosphorus 2b transport protein (NaPi2b) and is located on the apical side of the intestinal lumen. This protein is expressed when low serum phosphorus increases parathyroid hormone (PTH) concentrations which then stimulates production of activated vitamin D3. Similarly, high serum phosphorus concentrations increase fibroblast growth factor 23 (FGF23) concentrations and lower PTH concentrations which reduce active vitamin D3 production and decrease NaPi2b production (7). Paracellular phosphorus absorption is an inactive transport that is mediated by the sodium/hydrogen exporter isoform 3 (NHE3) protein. This is thought to be a more potent controller of phosphorus absorption and a better target for directed drug therapy (8).

The focus of this review and the novelty of this work is on one such drug therapy product, the first novel NHE3 inhibitor to be studied in human subjects for the treatment of hyperphosphatemia, tenapanor hydrochloride. Tenapanor, a minimally systemically absorbed molecule, is an inhibitor of intestinal NHE3 that was developed to treat irritable bowel syndrome with constipation but that also lowers serum phosphorus by blocking its paracellular transport from the intestinal lumen. Tenapanor reduces intestinal phosphate absorption predominantly through reduction of passive paracellular phosphate flux. Tenapanor also prevents active transcellular phosphate absorption compensation by decreasing the expression of NaPi2b (9).

METHODS

To complete this narrative review, a search of the literature was conducted using PubMed and ClinicalTrials.gov search engines. The search term “tenapanor hyperphosphatemia” was used for both search engines. Results were limited to studies published in the English language and excluded review articles. Human, animal, and in vitro studies were included. No date range was specified.

RESULTS

Using the search methods described above, 17 articles were returned. After excluding review articles, 11 primary studies were identified. All phase one through phase three articles were included in our review for completeness. Another 11 studies are currently recruiting patients, underway, or do not have published results. Of the published trials, the largest study in humans enrolled 236 patients. Most studies evaluated the efficacy of tenapanor for hyperphosphatemia while others focused on drug-drug interactions. Table 1 depicts a summary of the details and findings obtained from the described search method.

DISCUSSION

Phase one trials were included in this review to thoroughly examine tenapanor’s effect on hyperphosphatemia and potential drug-drug interactions. These drug-drug interactions are a crucial part of clinical practice and in the case of tenapanor involve CYP450 inhibition, phosphate binders, and PepT1. All three drug interaction studies in vivo concluded that there was no difference in serum concentrations of the test drug and tenapanor when both were co-administered (10-12). It is important to note that there is no drug-drug interaction between phosphate binders and tenapanor, as dual therapy with these agents may be warranted with tenapanor in patients with persistent hyperphosphatemia.

A few publications included data from in vitro, animal, and human studies together. Some outcomes from the in vitro and animal studies in those select publications did not translate into the same results in vivo. For example, one study considered that tenapanor, although minimally systemically absorbed, may exhibit drug-drug interactions with CYP450 enzymes since CYP3A4 is also present in the cells of the gut wall. In vitro studies displayed inhibition of CYP3A4 by tenapanor. However, no such interaction was observed from the co-administration of midazolam (a model substrate of CYP3A4) and tenapanor in human studies (10). This phenomenon could possibly be due to a higher concentration of tenapanor used in vitro compared to that found in human intestinal tissue.

All the phase three trials had a primary endpoint of change in serum phosphorus concentrations from baseline in patients suffering from hyperphosphatemia. The proportion of patients that reached a serum phosphorus concentration of < 5.5 mg/dL were only included as a secondary endpoint (13, 14). Normal serum phosphorus concentrations are between 2.5 and 5.5 mg/dL.
<table>
<thead>
<tr>
<th>Authors, Year</th>
<th>Study Designs and Objective(s)</th>
<th>Patients (if applicable)</th>
<th>Treatment Drug(s) and Dose</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labonte et al., 2015 (21)</td>
<td>Animal study</td>
<td>Obj: Evaluate the effect of tenapanor on dietary phosphorus absorption in rats</td>
<td>N = 9 male Sprague-Dawley rats</td>
<td>Tenapanor 0.3, 1, and 3 mg/kg</td>
</tr>
<tr>
<td>King et al., 2020 (22)</td>
<td>Animal study</td>
<td>Obj: Evaluate the effect of tenapanor and varying doses of sevelamer carbonate on urinary phosphorus excretion in rats</td>
<td>N = 102 8-week-old male Sprague-Dawley rats</td>
<td>Tenapanor 0.15 mg/kg BID + Sevelamer 0.75% to 3% (wt/wt)</td>
</tr>
<tr>
<td>Johansson et al., 2017 (10)</td>
<td>In vitro study</td>
<td>Obj: Determine if tenapanor inhibits various CYP450 enzymes</td>
<td>N/A</td>
<td>Tenapanor 0.1, 0.3, 1.0, 3.0, 10, and 30 μM in the presence of CYP enzyme marker substrates and NADPH</td>
</tr>
<tr>
<td>Johansson et al., 2017 (11)</td>
<td>In vitro study</td>
<td>Obj: Determine if tenapanor induces CYP1A2, CYP2B6, or CYP3A4 via mRNA expression</td>
<td>N/A</td>
<td>Tenapanor 0.0001 to 50 μM</td>
</tr>
<tr>
<td></td>
<td>Phase 1: Open label</td>
<td>Obj: Determine if tenapanor clinically inhibits or induces CYP3A4</td>
<td>N = 28 healthy volunteers</td>
<td>Midazolam 7.5 mg single dose + Tenapanor 15 mg BID</td>
</tr>
<tr>
<td></td>
<td>Animal Study</td>
<td>Obj: Determine the pharmacodynamic effects of coadministration of tenapanor with phosphate binders</td>
<td>N/A</td>
<td>Tenapanor 1, 10, 50, 100, and 200 μM + Sevelamer carbonate 1.6 mg/mL, calcium acetate 1 mg/mL, and calcium carbonate 2.4 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Obj: Determine the in vivo effects of coadministration of tenapanor with phosphate binders</td>
<td>N = 60 7-week-old male Sprague-Dawley rats</td>
<td>Tenapanor dissolved in water at 0.1, 0.3, 1, or 3 mg/kg + Sevelamer carbonate dissolved in water at 48 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Phase 1: Open-label, crossover</td>
<td>Obj: Determine the clinical effects of coadministration of tenapanor with phosphate binders</td>
<td>N = 16 healthy volunteers</td>
<td>Tenapanor 15 mg BID x 4 days + sevelamer 800 mg TID x 4 days 2-day washout before crossover with sevelamer or Ca based binder</td>
</tr>
</tbody>
</table>

Table 1. (continued)
Johansson et al., 2017 (12)  
Phase 1: Open-label, crossover  
Obj: Determine tenapanor’s effect on PepT1 activity in healthy volunteers  
N = 28 healthy volunteers  
Single dose cefadroxil 500 mg in AM for 1 day + Tenapanor 15 mg BID x 4 days, followed by single doses of both tenapanor 15 mg and cefadroxil 500 mg on day 5  
4-day washout between treatments  
Cefadroxil plasma concentration-time curves were similar whether cefadroxil was administered alone or in combination with tenapanor. PK parameters also similar when cefadroxil was given alone or with tenapanor indicating no effect on PepT1’s absorption activity.

Johansson et al., 2017 (23)  
Phase 1: RCT  
Obj: To report on the safety and efficacy of tenapanor on healthy subjects  
N = 83 healthy adults  
Tenapanor 180 mg single dose or 15, 30, 60, or 90 mg BID x 7 days  
Diarrhea and abdominal pain were the most common AEs related to treatment. Repeated doses of tenapanor resulted in increased stool phosphorus and decreased urine phosphorus. All tenapanor doses Table 1. (continued) resulted in plasma concentrations below lower limit of quantification suggesting low systemic absorption. Tenapanor produces its effect by tight-junction modulation which increases transepithelial electrical resistance and reduces permeability to phosphate, reducing paracellular phosphate absorption. Tenapanor prevents active transcellular phosphate transport by decreasing NaPi2b expression.

King et al., 2018 (8)  
Animal Studies  
Obj: Determine the mechanism by which tenapanor reduces gastrointestinal phosphate uptake  
N = 5 to 7 healthy rats per group in each experiment  
Various tenapanor doses based on the experiment performed  
Tenapanor produces its effect by tight-junction modulation which increases transepithelial electrical resistance and reduces permeability to phosphate, reducing paracellular phosphate absorption. Tenapanor prevents active transcellular phosphate transport by decreasing NaPi2b expression.

Block et al., 2017 (16)  
Phase 2: RCT, dose-ranging  
Obj: Evaluate the effect of tenapanor on serum phosphate concentration in HD patients with hyperphosphatemia  
N = 162 CKD stage 5D adults on maintenance HD with hyperphosphatemia  
Tenapanor 3 or 30 mg daily; or 1, 3, 10, or 30 mg twice daily for 4 weeks  
Statistically significant dose-dependent reduction in serum phosphate with largest reductions in the tenapanor 10 and 30 mg BID groups  
No significant difference in serum PTH

Block et al., 2019 (24)  
Phase 2b: RCT  
Obj: Evaluate the effect of tenapanor on serum FGF23  
N = 162 CKD stage 5D patients receiving HD on stable dose of phosphate binders with hyperphosphatemia  
Tenapanor 3 or 30 mg daily; or 1, 3, 10, or 30 mg twice daily  
Tenapanor treatment decreased serum FGF concentrations from post-phosphate binder washout. FGF23 continued to rise in patients receiving placebo after washout.

Table 1. (continued)
Reducing a patient’s serum phosphorus levels to < 5.5 mg/dL would be what is clinically significant rather than merely recognizing a change in serum phosphorus from baseline. The ongoing NORMALIZE (NCT03988920) trial is studying this clinical significance, as its primary endpoint is the proportion of patients who reach a normal serum phosphorus concentration (2.5-5.5 mg/dL) (15). Only one clinical study, AMPLIFY, has tested the combination of tenapanor with phosphate binder therapies. Phosphate binders tested included sevelamer and non-sevelamer binders. The study investigators did not include which binders comprised the non-sevelamer group. Tenapanor + binder resulted in a significantly larger decrease in serum phosphorus compared to placebo + binder (-0.84 vs. -0.19 mg/dL; P < 0.001) (14). No tenapanor monotherapy group was included in the study design and no definitive statement can be made regarding the additive or synergistic effect of tenapanor. It is likely that given the complementary mechanism of action that some degree of synergy may exist.

All clinical trials in human subjects published to date have been conducted in ESKD patients receiving maintenance hemodialysis. There is evidence that tenapanor as monotherapy as well as given concomitantly with phosphate binders lowers serum phosphorus levels. Hemodialysis patients currently taking phosphate binders with uncontrolled hyperphosphatemia may benefit from tenapanor to reduce the pill burden of phosphate binders. Adherence with phosphate binders was low at 38% and phosphate binders accounted for half of a patient’s total pill burden (16). 70% of patients on hemodialysis continued to experience elevated serum phosphorus despite efforts to control levels through diet and phosphate binder therapy (14). Tenapanor has been dosed between 10-30 mg twice daily without regard to meals in the studies presented here. This dosing schedule and pill burden could be considerably less than those for phosphate binders since phosphate binders require administration three times daily with meals. This drug’s twice daily dosing can be a benefit for patients suffering from excessive pill burden. Although not specifically studied in humans, cardiovascular calcification would not be expected with tenapanor compared to other calcium-containing phosphate binders such as calcium carbonate as it does not contain calcium. From the evidence presented, it appears tenapanor as an adjunct therapy to phosphate binders produces the greatest decrease in serum phosphorus concentrations (14). Monotherapy with tenapanor also lowers serum phosphorus although not to the same degree as dual therapy. The ongoing NORMALIZE trial is evaluating the ability of
tenapanor alone or in combination with sevelamer to achieve normal serum phosphorus concentrations in patients with ESKD (15). Once published, this information will further guide clinicians in the appropriate use of tenapanor. It is important for prescribers to know and share with patients that diarrhea (16%), flatulence, and abdominal distention (3% each) have been the most common adverse effects of tenapanor. The drug is contraindicated for use in children < 6 years old and in patients with intestinal obstruction (17-19).

In July 2021, the Food and Drug Administration (FDA) issued a Complete Response Letter to the pharmaceutical company Ardelyx, the makers of tenapanor, and stated that more significant clinical data was needed before approval could be granted for the indication of hyperphosphatemia. Although the current data does show a reduction in phosphorus serum concentrations, the magnitude of this effect requires more investigation (20).

CONCLUSION

In conclusion, tenapanor has shown a unique mechanism of action to reduce phosphate absorption from the intestines, thus further reducing serum phosphorus concentrations in patients. Published data to date show efficacy as monotherapy and a greater effect when combined with phosphate binders. When used as monotherapy, this may reduce excessive pill burden from phosphate binders. No significant drug interactions have been observed clinically, and tenapanor can be administered without regard to meals. The long-term safety of tenapanor is unknown as well as its efficacy in CKD patients who are not on hemodialysis. More large, randomized trials regarding the use of tenapanor, powered for cardiovascular and/or mortality outcomes, in CKD as well as ESKD patients, are needed, especially for subpopulations that have not been adequately represented in previous trials. In addition, more data demonstrating the magnitude of the phosphorus lowering effect will be needed before FDA approval is granted to tenapanor for treating hyperphosphatemia.

ACKNOWLEDGEMENTS

The authors have nothing to disclose regarding the preparation of this work and have not received financial support of any kind.

REFERENCES


