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Review

Effectivity and safety profile of tenapanor, a sodium-hydrogen exchanger isoform 3 inhibitor, as an innovative treatment for hyperphosphatemia in chronic kidney disease: A systematic review of clinical studies

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ABSTRACT

Background: Chronic kidney disease (CKD) is a major global health problem. Hyperphosphatemia is frequent in CKD and a reason for increased morbidity and mortality as it generates hyperparathyroidism, high fibroblast growth factor 23 (FGF23), and hypocalcemia. Available hyperphosphatemia therapies still have limitations, including risk of metal overload, cardiovascular calcification, and systemic adverse effects (AEs). Tenapanor is a new hyperphosphatemia treatment in CKD with sodium-hydrogen exchanger isoform 3 (NHE3) inhibition mechanism and low systemic AEs.

Objectives: Discovering the effectivity and safety of tenapanor as hyperphosphatemia management in CKD.

Method: Literature searching is performed by using “pubmed” and “science direct” with “tenapanor”, “chronic kidney disease”, and “hyperphosphatemia” as keywords. The literatures were selected using PRISMA algorithm version 2020. Literature was screened based on Population, Intervention, Comparison, and Outcome (PICO) criteria which are: CKD patients requiring dialysis as population, tenapanor or its combination with dialysis or phosphate binders as intervention, placebo or other phosphate binders without tenapanor as comparison, and serum phosphate, safety profile, and other pleiotropic benefits related to hyperphosphatemia management as the outcome. The included studies then assessed for risk of bias and qualitatively reviewed.

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Outcome: Tenapanor was able to reduce serum phosphate, generally in a dose-dependent manner. Tenapanor also suppressed FGF23 and parathyroid hormone, probably due to decreased serum phosphate. The frequent AEs were transient mild-to-moderate diarrhea in a dose-dependent manner. Tenapanor was generally well-tolerated with low systemic AEs due to its non-calcium, metal-free, and low-absorbed properties.
Conclusion: Tenapanor is an effective and safe option for hyperphosphatemia management in CKD.

Perfil de efectividad y seguridad de tenapanor, un inhibidor de la isoforma 3 del intercambiador de sodio/hidrógeno, como tratamiento innovador para la hiperfosfatemia en la enfermedad renal crónica, una revisión sistemática de estudios clínicos

Palabras clave:
Enfermedad renal crónica
Hiperfosfatemia
Tenapanor

RESUMEN

Antecedentes: La enfermedad renal crónica (ERC) es un importante problema de salud mundial. La hiperfosfatemia es frecuente en la ERC y motivo de aumento de la morbimortalidad ya que genera hiperparatiroidismo, *fibroblast growth factor-23* (FGF-23), elevado e hipocalcemia. Las terapias disponibles para la hiperfosfatemia aún tienen limitaciones, incluido el riesgo de sobrecarga de metales, calcificación cardiovascular y efectos adversos (EA) sistémicos. Tenapanor es un nuevo tratamiento de la hiperfosfatemia en la ERC con mecanismo de inhibición de la isoforma 3 del intercambiador de sodio-hidrógeno (NHE3) y EA sistémicos bajos.
Objetivos: Descubrir la efectividad y la seguridad del tenapanor como manejo de la hiperfosfatemia en la ERC.
Método: La búsqueda bibliográfica se realiza utilizando «Pubmed» y «Science direct» con «tenapanor», «chronic kidney disease» e «hyperphosphatemia» como palabras clave. La selección de la literatura se realizó mediante el algoritmo PRISMA versión 2020. La bibliografía se examinó con base en los criterios de Población, Intervención, Comparación y Resultado (PICO, por sus siglas en inglés), que son: pacientes con ERC que requieren diálisis como población, tenapanor o su combinación con diálisis o quelantes de fosfato como intervención, placebo u otros quelantes de fosfato sin tenapanor como comparación, y fosfato sérico, perfil de seguridad y otros beneficios pleiotrópicos relacionados con el manejo de la hiperfosfatemia como resultado. A continuación, los estudios incluidos evaluaron el riesgo de sesgo y se revisaron cualitativamente.
Resultado: Tenapanor fue capaz de reducir el fosfato sérico, generalmente de una manera dosis/dependiente. Tenapanor también suprimió FGF-23 y la hormona paratiroidea, probablemente debido a la disminución del fosfato sérico. Los EA frecuentes fueron diarrea transitoria leve a moderada de manera dosis/dependiente. En general, el tenapanor fue bien tolerado con EA sistémicos bajos debido a sus propiedades no cálcicas, libres de metales y de baja absorción.
Conclusión: Tenapanor es una opción eficaz y segura para el manejo de la hiperfosfatemia en la ERC.

Introduction

Chronic kidney disease (CKD) is still a major global health problem, with approximately 697.5 million people worldwide were reported to have CKD in 2017, of which 1.2 million people died due to CKD.[1] Hyperphosphatemia is often found in CKD. Declined renal function, particularly in the advanced stage will lead to serum phosphate accumulation due to an inability to excrete serum phosphate which mostly originates from daily intestinal absorption. Osteocytes then release fibroblast growth factor 23 (FGF23) in order to promote renal phosphate excretion. Unfortunately, FGF23 also impair renal 1.25-dihydroxycalcitriol production which disturb intestinal calcium absorption, resulting in hypocalcemia. Parathyroid glands then release parathyroid hormone (PTH) as a

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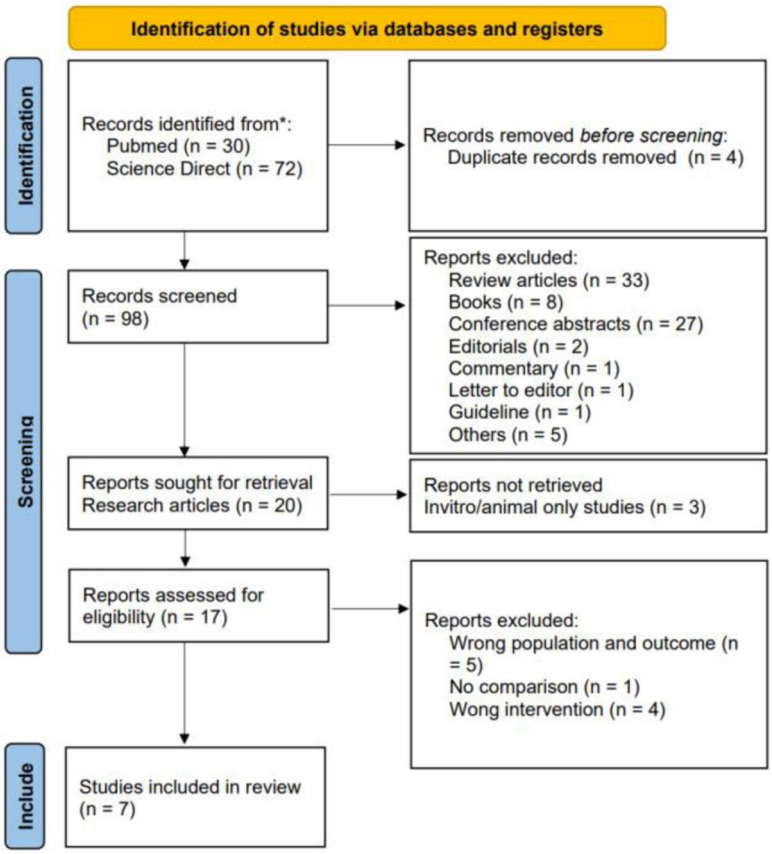

Fig. 1 – Literature screening algorithm by using "The Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) version 2020.

compensatory mechanism to increase serum calcium through bone resorption. Calcium and phosphate release from destructed bone will lead to cardiovascular calcification and bone disorders, thus increasing morbidity and mortality in patients with CKD.[2,3]

Dialysis, phosphate binders, and calcimimetic agents are available modalities for hyperphosphatemia management in CKD, but they still have some disadvantages including flexibility limitation, hypocalcemia risk, as well as metal overload and cardiovascular calcification.[4–6] Tenapanor is a novel modality option for hyperphosphatemia in CKD with its mechanism which inhibit sodium-hydrogen exchanger isoform 3 (NHE3) in gastrointestinal tract. This new medication has also been indicated for irritable bowel syndrome with constipation (IBS-C).[7,8] In this review, we provide clinical evidences of the effectivity and safety profile of tenapanor in managing hyperphosphatemia in CKD through its NHE3 inhibition.

Method

Literature searching was performed in Pubmed and Science Direct by using "tenapanor", "chronic kidney disease", and "hyperphosphatemia" as keywords. The studies then systematically selected by using The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) algorithm (Fig. 1). Duplicate literatures were removed. Review articles, books, conferences abstracts, editorials, commentaries, letter to editor, and guidelines were excluded, while research studies were retrieved. Literature screening was performed by using Population, Intervention, Comparison, and Outcome (PICO) criteria which are: CKD patients requiring dialysis as population, tenapanor or its combination with dialysis or phosphate binders as intervention, placebo or other phosphate binders without tenapanor as comparison, as well as serum phosphate and safety profile as the outcome. Studies which meet the criteria then examined for risk of bias as quality assessment and qualitatively synthesized to establish this systematic review.

Result

Risk of bias assessment in included studies

Our included studies have a relatively similarities in risk of bias. The participants and investigators were all blinded in all of our included studies.[9–15] There are two studies with unclear risk of randomization sequence method as it was not mentioned in the studies.[10,12] Five of included studies have unclear risk of concealment of randomization allocation.[10,12–15] All of our included studies have a low risk of bias in completeness of reported outcomes.[9–15] The general summary of the risk of bias in our included studies can be seen in Fig. 2.

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Fig. 2 – Risk of bias assessment of included studies.

Characteristics of included studies

A total of seven clinical studies were included in our review. All the studies evaluated the decrease of serum phosphate as their primary outcome.[9–15] Four studies use tenapanor or placebo alone as the intervention and comparison by implementing "washout system",[9–12] while the three other studies still maintained the previous phosphate binders as a combination with tenapanor or placebo.[13–15] Six of seven studies also examined FGF23 levels as the other outcome.[10–13,15,16] The level of PTH was investigated in two studies.[11,15] All of our included studies evaluated the safety profile of tenapanor. The summary of our included studies is described in Table 1.

The role of tenapanor as hyperphosphatemia treatment in chronic kidney disease

Hyperphosphatemia is a frequent metabolic complication of CKD, particularly in end stage disease. This complication is a result of impaired renal function and limitation of conventional dialysis to eliminate serum phosphate originated from dietary phosphate absorption.[9,12]

Tenapanor is a selective inhibitor of the sodium-hydrogen exchanger isoform 3 (NHE3), an antiporter located on the surface of the gastrointestinal tract's enterocytes. By inhibiting the sodium-hydrogen exchange, tenapanor causes the accumulation of intracellular protons and subsequently lowers the pH. This decrease in pH alters the tight junction proteins,

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Table 1 – Table of included studies.

Authors, years	Study design	Population	Intervention (I) and comparison (C)	Outcomes
Pergola et al., 2021	Multicenter, double blind, randomized placebo-controlled trial (RCT), phase 3	N = 235. CKD patients receiving regular hemodialysis (HD) with hyperphosphatemia.	I: Oral tenapanor 30 mg twice daily (BID) + pre-existing phosphate binder. C: Oral placebo BID + pre-existing binder. There was no follow-up visit in this study.	Significantly larger change in serum phosphorus from baseline (baseline phosphate levels: 6.7 mg/dL for tenapanor + binder group and 6.9 mg/dL for placebo + binder group) to week 4 in tenapanor + binder group (mean change from baseline: −0.84 mg/dL) compared to placebo + binder (mean change from baseline: −0.19 mg/dL), $p < 0.001$. Significantly larger proportion of patients achieved serum phosphorus < 5.5 mg/dl in tenapanor + binder group compared to placebo + binder ($p < 0.01$). Significant FGF23 reductions in tenapanor + binder group ($p = 0.003$). Transient mild to moderate diarrhea was the most common adverse effect (AE) with tenapanor + binder, resolved with dose adjustment. No clinical meaningful change in laboratory, electrocardiogram (ECG), and physical examination. No serious AE and death were related to treatment.
Block et al., 2019	Double blind, RCT, phase 3. Consists of randomized treatment period (RTP) and randomized withdrawal period (RWP)	N = 164 in RTP, 152 in RWP. Patients with end stage kidney disease (ESKD) receiving maintenance HD.	RTP (8 weeks): I: tenapanor regimens—3 or 10 mg fixed dose BID, or 30 mg BID which could be titrated. C: -RWP (4 weeks): I: previously assigned dose of tenapanor C: placebo	RTP: significant decreased serum phosphate ($p < 0.001$) in all three tenapanor groups (mean change −2.48 mg/dL, −2.52 mg/dL, and −2.61 mg/dL for tenapanor 3 mg BID, 10 mg BID, and 30 mg BID titration, respectively) from baseline (7.40 ± 1.57 mg/dL, 7.46 ± 1.69 mg/dL, and 7.62 ± 1.43 mg/dL for tenapanor 3 mg BID, 10 mg BID, and 30 mg BID titration, respectively). Reduction of FGF23 in all three tenapanor groups, significant reduction observed in the 3 and 30 mg BID. RWP: significant change in serum phosphate between pooled tenapanor group (mean change +0.56 mg/dL) compared to placebo (mean change +1.38 mg/dL), $p = 0.003$. Diarrhea was the most common AE. There was no treatment discontinuation in RWP. There was no clinically meaningful change in laboratory, ECG, and physical examination. There was no death related to treatment.

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Table 1 – (*Continued*)

Authors, years	Study design	Population	Intervention (I) and comparison (C)	Outcomes
Block et al., 2017	Multicenter, double blind, RCT	N = 162 Patients with ESKD receiving maintenance HD with hyperphosphatemia	I: one of six tenapanor regimens (3 or 30 mg once daily or 1, 3, 10, or 30 mg BID) C: placebo. Follow-up period after last dosage: 1–2 weeks	Baseline phosphate levels were 7.32–7.92 mg/dl in tenapanor groups and 7.87 mg/dl in placebo group. Tenapanor resulted in dose-dependent reduced serum phosphate from baseline compared to placebo (mean change from baseline in the end of treatment were −1.21, −1.18, −1.28, −1.93, −2.41, −1.85, and −2.67 mg/dL for placebo, tenapanor 1 mg BID, 3 mg once daily, 3 mg BID, 10 mg BID, 30 mg once daily, and 30 mg BID, respectively). Largest reductions were found in the tenapanor 10 and 30 mg BID compared to placebo ($p < 0.05$). At 1–2 weeks follow-up visit, serum phosphate were still maintained between 3 and 6 mg/dL for all groups. Proportion of patients reached serum phosphate < 5.5 mg/dL in tenapanor was up to 43%, while in placebo only 8%. Significant FGF23 reduction in all tenapanor groups compared to placebo ($p < 0.05$). The most frequent AE was GI symptoms (diarrhea), mostly mild to moderate. Severe diarrhea predominantly found in tenapanor 30 mg once or twice daily. No serious AE was related to the treatment. No clinically relevant changes in serum calcium, potassium, or sodium.
Shigematsu et al., 2021	Multicenter, double blind, RCT.	N = 47 CKD patients receiving HD with hyperphosphatemia.	I: Tenapanor 30 mg BID + pre-existing phosphate binders. C: Placebo + pre-existing phosphate binders. There was no follow-up visit in this study.	Mean baseline serum phosphate were 7.01 mg/dL and 6.77 mg/dL in placebo and tenapanor 30 mg titration, respectively. Larger serum phosphate decrement in tenapanor (mean change −1.5 mg/dL) compared to placebo group (mean change −0.5 mg/dL). Target achievement of phosphorus < 5.5 mg/dL was 73.9% with tenapanor + binder and 25% in placebo + binder. Dominant AE was GI symptoms especially transient non-severe diarrhea. There were no significant changes in laboratory, vital signs, or ECG. There was no serious AE and death related to treatment.

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Table 1 – (*Continued*)

Authors, years	Study design	Population	Intervention (I) and comparison (C)	Outcomes
Inaba et al., 2021	Multicenter, double blind, RCT, phase 2.	N = 207 CKD patients receiving HD with hyperphosphatemia.	I: Tenapanor 5-mg BID, 10-mg BID, 30-mg BID, and 30-mg BID with dose titration. Dose adjustment was only for dose-titration group. C: placebo Second withdrawal period after last dosage: 3 weeks	Baseline serum phosphate were 7.6 mg/dl, 7.5 mg/dl, 8.1 mg/dl, 7.7 mg/dl, and 7.4 mg/dl for placebo, tenapanor 5 mg BID, 10 mg BID, 30 mg BID, and 30 mg dose titration respectively. Significantly reduced serum phosphate in each tenapanor dosage groups compared to placebo (mean change: −0.9 mg/dL, −1.4 mg/dL, −1.9 mg/dL, −2.0 mg/dL, and +0.6 mg/dL for tenapanor 5 mg BID, 10 mg BID, 30 mg BID, 30 mg BID with dose titration, and placebo respectively), $p < 0.001$. Serum phosphate were back near baseline levels after the end of the treatment period for all intervention groups in the study. No significant changes in serum Ca in any group. Intact PTH and FGF23 decreased in tenapanor groups. Mild to moderate diarrhea was the most frequent AE and it was dose-related, mostly in 30 mg BID group. There was no severe diarrhea in tenapanor groups. No clinically relevant alterations in vital signs, laboratory, or electrocardiogram. There were no deaths during the study.
Block et al., 2019	Multicenter, double blind, RCT, phase 2B.	N = 162 Patients with ESKD receiving HD with hyperphosphatemia.	I: One of six tenapanor regimens (3 or 30 mg once daily, or 1, 3, 10 or 30 mg BID). C: placebo. There was no follow-up visit in this study.	Serum phosphate after wash-out period were 7.32–7.92 mg/dL in tenapanor group and 7.87 mg/dL in placebo group. Tenapanor decrease serum phosphate in dose-dependent manner compared to placebo (least-squares mean changes: tenapanor-treated groups, −0.47 to −1.98 mg/dL; placebo group, −0.54 mg/dL; $p = 0.01$). Highest serum phosphate reduction was in tenapanor 10 and 30 mg BID ($p < 0.05$ for each groups vs placebo). FGF23 was significantly reduced in range of 2030–3563 pg/mL in all tenapanor groups ($p < 0.001$–0.04), while FGF23 continued to increase in placebo group. Tenapanor dose of at least 3 mg per day was needed to significantly reduce FGF23. GI disorders (diarrhea) was the common AE, particularly in high tenapanor groups of 10 BID, 30 mg once daily, and 30 mg BID.
Nitta et al., 2023	Double blind, RCT, phase 3.	N = 169 CKD patients receiving HD with hyperphosphatemia.	I: Tenapanor 5 mg BID + pre-existing phosphate binders. C: Placebo + pre-existing phosphate binders. There was no follow-up visit in this study.	Baseline serum phosphate were 6.92 ± 1.068 mg/dL and 6.76 ± 1.075 mg/dL in placebo + other phosphate binders and in tenapanor + other phosphate binders groups. Significantly reduced serum phosphate from baseline in tenapanor + other phosphate binders group compared to placebo + other phosphate binders group (mean change −2.00 mg/dL vs −0.24 mg/dL), $p < 0.0001$. Higher proportion of serum phosphate target achievement in tenapanor compared to placebo. Serum FGF and PTH were significantly decreased in the tenapanor group, while increased in placebo group. Diarrhea was the dominant AE, all were mild to moderate. There was no treatment discontinuation due to diarrhea.

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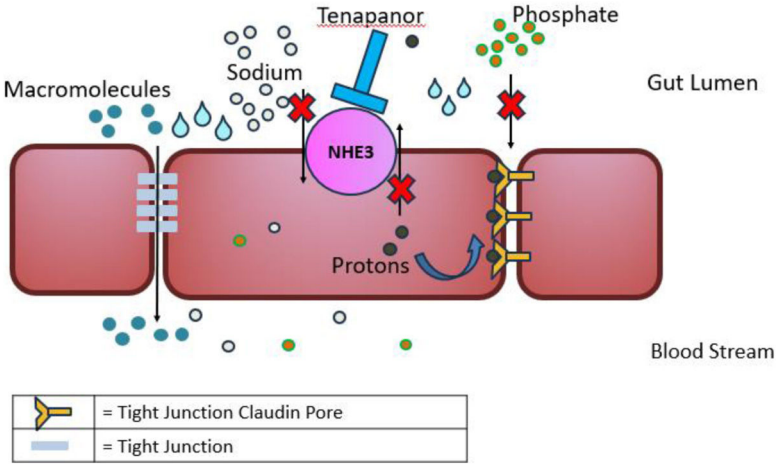

Fig. 3 – Tenapanor, mechanism of action.

resulting in a decrease in the permeability of phosphate paracellular diffusion and ultimately lowering the level of serum phosphate.[9–11,14] The mechanism of tenapanor in inhibiting phosphate absorption can be seen in Fig. 3.

Effectivity of tenapanor in lowering serum phosphate in chronic kidney disease

There are four studies which investigated the effect of tenapanor as a single therapy to serum phosphate in CKD patients. All the patients underwent 1–3 weeks of washout period before started the treatment.[9–12] The majority dose of tenapanor was 3, 10, and 30 mg twice daily (BID),[9–12] though dosage of 3 and 30 mg once daily[10,12] as well as 1 and 5 mg BID was also found.[10–12] All these studies showed a higher decrease in serum phosphate with tenapanor as a single therapy compared to placebo.[9–12] Significant serum phosphate decrement from baseline was reported with tenapanor dose of 3, 5, 10, and 30 mg BID in fixed dose as well as 30 mg BID with titration versus placebo in two studies.[9–11] Tenapanor reduces serum phosphate levels in a dose-dependent manner in all four studies.[9–12] In the other hand, tenapanor as single therapy also resulted in higher proportion of patients achieving serum phosphate target of <5.5 mg/dL compared to placebo.[10]

Serum phosphate before the administration of tenapanor and placebo in studies which examined tenapanor effectivity as monotherapy ranged from 7.32 to 8.1 mg/dL.[9–12] The lowest serum phosphate reduction was found in tenapanor 1 mg BID that ranged from −0.47 mg/dL[12] to −1.18 mg/dL.[10] Administration of tenapanor 3 mg BID resulted in serum phosphate change of −1.93 mg/dL[10] to −2.48 mg/dL,[9] while tenapanor 3 mg once daily only decreased serum phosphate up to −1.28 mg/dL.[10] Tenapanor dosage of 5 mg BID was only found in one study which only showed serum phosphate reduction of −0.9 mg/dL.[11] Tenapanor dosage of 30 mg once daily resulted in serum phosphate decline of −1.85 mg/dL.[10] Serum phosphate reduction in tenapanor 30 mg BID is similar between the non-dose-titration group and those with dose-titration.[10,11] In tenapanor 30 mg BID without dose titration, the serum phosphate reduction ranged from −1.97 mg/dL[11] to −2.67 mg/dL,[9] while in tenapanor 30 mg BID with dose titration, the serum phosphate decline ranged from −2.0 mg/dL[11] to −2.61 mg/dL.[9]

Efficacy of tenapanor as a combination therapy with other phosphate binders was observed in three studies. All the subjects in the studies maintained their pre-existing phosphate binders which then added with tenapanor or placebo.[13–15] The serum phosphate in three studies that used a combination of tenapanor and other phosphate binders as a treatment regimen before the intervention ranged from 6.7 to 7.01 mg/dL.[13–15] The dose of tenapanor used in these studies are not as variable as in studies that used tenapanor as monotherapy. Two of three studies use tenapanor 30 mg BID as the treatment,[13] while one study use tenapanor 5 mg BID.[15] In all three studies, the combination of tenapanor with phosphate binders revealed a greater reduction of serum phosphate compared to the combination of placebo with phosphate binders.[13–15] Statistical significance was found in two of three studies with tenapanor dose of both 5 mg BID and 30 mg BID.[13,15] In two studies of tenapanor 30 mg BID as combination with other phosphate binders, the mean change of serum phosphate declined were −0.84 mg/dL[13] and −1.5 mg/dL,[14] while in study of tenapanor 5 mg BID combined with other phosphate binders, the mean change of serum phosphate were up to −2.0 mg/dL.[15] A higher rate of target achievement for serum phosphate was also found in tenapanor group compared to placebo in all three studies[13–15], in which two of three studies set the serum phosphate target to <5.5 mg/dL,[13,14] while serum phosphate goal ranged from 3.5 to 6.0 mg/dL in one other study.[15]

Besides observing direct effect of tenapanor to serum phosphate, three of four studies which used tenapanor as monotherapy also evaluated the impact of tenapanor to serum phosphate in certain duration after the last administration of tenapanor.[9–11] In a randomized withdrawal period in a study by Block et al. in 2019, participants that had previously been treated with tenapanor then continued with placebo for 4 weeks experienced an increase in serum phosphate with mean change of +0.07 mg/dL.[9] In the follow-up visit 1–2 weeks after the last intervention in the study by Block et al. in 2017, the serum phosphate was still maintained between 3 and

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6 mg/dL in all intervention groups, including tenapanor with various dosages.[10] A study by Inaba et al. revealed that serum phosphate levels returned to near baseline levels 3 weeks after the last administration of both the full dosage of tenapanor and placebo.[11]

Pleiotropic effect of tenapanor in interfering fibroblast growth factor 23 and parathyroid hormone in chronic kidney disease

Besides reducing serum phosphate, tenapanor was also found to have a beneficial effect on FGF23 and PTH levels. A total of six studies showed FGF23 declined with tenapanor.[10–13,15,16] Significant decrease in FGF23 was observed in tenapanor as single therapy at dose of 1, 3, 10, and 30 mg BID as well as 3 and 30 mg once daily.[9,10,12] Tenapanor as a combination therapy with other phosphate binders also showed its ability to reduce FGF23 levels at doses of both 5 mg and 30 mg BID.[13,15]

Tenapanor was also found to suppress PTH levels other than serum phosphate and FGF23 in two studies.[11,15] As monotherapy, tenapanor at dose of 5, 10, and 30 mg BID was able to reduce PTH levels though the significance was not reported.[11] In a setting as combination therapy with other phosphate binders, tenapanor 5 mg BID was reported to significantly suppress PTH.[15]

Safety profile of tenapanor in chronic kidney disease population

Safety profile of tenapanor was evaluated in all of our included studies.[9–15] Gastrointestinal symptoms especially diarrhea was the most frequent adverse effect (AE) in all the studies.[9–15] The intensity of diarrhea was dominantly mild to moderate in severity with transient onset in majority of studies.[13–15] In the setting of tenapanor as single therapy, the diarrhea tended to be dose-dependent, as the incidence of diarrhea was higher in tenapanor dose of 10 mg and 30 mg BID as well as 30 mg once daily.[9–12] The same trend was also found in the setting of tenapanor as combination therapy with phosphate binders, in which higher incidence of diarrhea was reported in studies with higher dose of tenapanor.[13–15] Severe diarrhea was reported in one study, which is predominantly in tenapanor dose of 30 mg once and twice daily.[17]

The safety profile of tenapanor was also evaluated with physical examination, laboratory, and electrocardiography (ECG) parameters. In our included studies, tenapanor therapy didn't lead to any significant change in physical examination, laboratory, and ECG parameters. There was also no death related to tenapanor. From these findings, tenapanor was relatively safe and well tolerated in CKD patients.[9–11,13,14]

Discussion

Phosphate retention is frequently found in CKD stage 4 and 5, which is a factor that initiate many other disturbances such as increased FGF23 and PTH, hypocalcemia, and low vitamin D, which in turn will lead to an enhancement in cardiovascular and all causes of morbidity and mortality.[18] Phosphate balance is maintained by several mechanism including intestinal phosphate absorption, bone turnover regulation, as well as renal excretion and reabsorption.[4,19] In a normal condition, the kidney excretes approximately ninety percent of phosphate per day.[20] As renal phosphate clearance declined in CKD, inhibiting intestinal phosphate absorption can be a promising approach in managing hyperphosphatemia in patients with CKD.[4,20]

Generally, phosphate binders only result in maximum 2.0 mg/dL of phosphate reduction in their maximal doses.[9] Some of our included studies show that 30 mg of tenapanor whether as fixed or titrated dose single therapy was able to reduce serum phosphate up to more than 2.0 mg/dL.[9,10] This finding can be possible due to tenapanor mechanism which suppress intestinal phosphate absorption through NHE3 inhibition,[9–11,14] as about 90% of phosphate input comes from intestinal absoption.[20]

Tenapanor works by inhibiting NHE3 which then interferes with sodium and phosphate absorption in the intestinal lumen. By using this mechanism, tenapanor has a promising potency to effectively treat hyperphosphatemia in CKD due to its dominant role in gastrointestinal tract, as around 90% of phosphate are originated from intestinal absorption.[9–11]

Our included studies which used tenapanor as monotherapy commonly revealed a dose-dependent phosphate lowering effect.[9–12] Tenapanor 1 mg BID showed serum phosphate declined up to −1.18 mg/dL.[10,12] Administration frequency also influence the effectivity of tenapanor 3 mg, which reduce serum phosphate around −1.28 mg/dL in once daily dose[10] and up to −2.48 mg/dL in BID dose.[9,10] Tenapanor 10 mg BID was shown to reduced serum phosphate up to −2.52 mg/dL in several studies.[9–12] Tenapanor with dose of 30 mg also showed the same frequency-dependent manner in lowering serum phosphate, where twice daily dose resulted in up to −2.67 mg/dL serum phosphate reduction, while in once daily dose, the serum phosphate only decreased up to −1.85 mg/dL.[10] In the other hand, 30 mg BID tenapanor with dose titration exhibited an unsignificant difference in phosphate reduction effect compared to non-dose-titration administration of tenapanor 30 mg.[9,10] This finding suggest the possible strategy to achieve the highest serum phosphate reduction target by using tenapanor with optimum dose while minimizing the side effects by using dose-titration strategy.[9,10]

Unlike the studies that used tenapanor as monotherapy, the phosphate reduction trend is inconsistent with the dose in studies that used tenapanor in combination with other phosphate binders. Tenapanor 30 mg BID in combination with the patient's pre-existing phosphate binders resulted in −0.84 mg/dL phosphate reduction in a study by Pergola et al.[13] and −1.5 mg/dL reduction in a study by Shigematsu et al.[14] Meanwhile, in the study by Nitta et al., tenapanor 5 mg BID in combination with patient's pre-existing phosphate binder reduced the serum phosphate up to −2.0 mg/dL,[15] which was even higher than tenapanor 30 mg BID in studies by Pergola et al.[13] and Shigematsu et al.[14] This different trend can be possibly caused by the effect of other phosphate binders which could probably have any undiscovered interactions with tenapanor. Further studies which analyze the possible drug-drug interaction between tenapanor and other phosphate binders is needed to explore the exact possible results of combination

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therapy between tenapanor and other phosphate binders as hyperphosphatemia therapy for patients with CKD. However, until the time of this review is conducted, studies show that tenapanor as monotherapy has a better phosphate reduction effect compared to tenapanor as a combination therapy with other phosphate binders.[9–15]

Serum phosphate after the termination of tenapanor is also one of the concerns. In randomized withdrawal period in the study by Block et al. in 2019, patients receiving placebo for 4 weeks after the last dose of tenapanor experienced increasing serum phosphate of only +0.79 mg/dL.[9] In the study by Block et al. in 2017, the follow-up visit at 1–2 weeks after the last dosage of tenapanor showed that the serum phosphate of all groups were between 3 and 6 mg/dL which still didn't reach the baseline serum phosphate before the beginning of intervention.[10] In addition, a study by Inaba et al. revealed that serum phosphate levels were increased near baseline levels in follow-up visit after 3 weeks from the last dosage of tenapanor.[11] These findings suggest that serum phosphate maintenance after the last dosage of tenapanor can be variable, which could be possibly influenced by several factors such as the baseline serum phosphate which varies in these studies, duration since the last dosage of tenapanor which only 1–2 weeks in certain studies and up to 4 weeks in the other study, also the dosage and frequency of tenapanor administration, which implies the need for further studies to examine serum phosphate maintenance in more detailed period after the last dosage of tenapanor. However, from these studies, it can be concluded that serum phosphate can still be maintained at levels below the baseline, even until 3–4 weeks after the last dosage of tenapanor.[9–11]

In addition to its phosphate lowering effect, tenapanor was also found to have a pleiotropic effect in suppressing the levels of FGF23 and PTH, both as monotherapy and combination therapy with phosphate binders.[10–13,15,16] The exact mechanism of this finding remains unclear, but it can be possibly explained by the role of these two hormones as compensatory mechanism to elevated serum phosphate, thus greater reduction of serum phosphate will suppress FGF23 and PTH production.[9,11,12,15] This pleiotropic effect of tenapanor can be utilized to minimize the morbidity and mortality in CKD, as high FGF23 and PTH will cause extraosseous calcium and phosphate deposition, particularly in the heart valves and vascular. This condition then develop to valve and vascular atherosclerosis through osteochondrogenic differentiation and elastin degradation, leading to increased mortality due to cardiovascular disease.[21] Besides that, increased PTH which enhance calcium efflux from bones is the cause of bone mass loss in patients with CKD, resulting in increased morbidity.[22] Therefore, the pleiotropic effect of tenapanor in lowering FGF23 and PTH suggesting its potency as future treatment for bone mineral disease and secondary hyperparathyroidism in CKD.

Diarrhea is the most common AE caused by tenapanor. However, majority of reported diarrhea was transient and mild to moderate in intensity.[13–15] This side effect appears as the effect of tenapanor mechanism which selectively inhibit the NHE3 in enterocytes, thus suppress the passive transport of phosphate in the intestine. Simultaneously, NHE3 inhibition also suppress intestinal sodium absorption which enhance sodium and water secretion in the intestinal tract.[10,11] Elevated sodium, phosphate, and water content in the intestine then lead to loose stool and increased bowel movement which manifested as diarrhea.[9,15] The incidence of diarrhea due to tenapanor has a higher trend in higher doses.[9–15] Diarrhea side effect of tenapanor is no longer surprising, as tenapanor has also been indicated to treat IBS-C by its mechanism to increase water content in the intestinal lumen and stools. Utilization of tenapanor in IBS-C has been considered as safe and has been recommended by the American Gastroenterological Association (AGA) guideline.[7,8,23] Dose titration can be a good solution for this problem to increase patient's compliance, as titrated dose of tenapanor 30 mg BID exhibited a lower incidence of diarrhea while maintaining the same efficacy in reducing serum phosphate and FGF23 compared to fixed dose of tenapanor 30 mg BID.[11]

Minerals deposition and metabolic disturbances are the other concerns in treatment options for hyperphosphatemia in CKD. Available phosphate binders still has systemic mineral and metabolic disadvantages, such as calcium accumulation and increased calcification in calcium based phosphate binders, potential nervous system toxicity in aluminum based phosphate binders, iron overload in iron based phosphate binders, fat-soluble vitamins deficiency and acidosis risk in sevelamer based phosphate binders, as well as possible lanthanum deposits in lanthanum based phosphate binders.[4–6] Tenapanor comes as a solution to counteract these limitations, as tenapanor didn't cause any meaningful changes in serum calcium, laboratory parameters, ECG, and physical examination.[9–11,13,14] The plausible explanation for this finding is the nature of tenapanor as a calcium free non-metal phosphate reducer, thus it doesn't cause calcium and metal accumulation. In addition, tenapanor is also a minimally absorbed molecule, resulting in minimum systemic side-effect.[9,10]

Conclusion

In conclusion, tenapanor, as a single therapy or in combination with phosphate binders, was effective in managing hyperphosphatemia in CKD. It also has pleiotropic effects in interfering high FGF23 and PTH thus exhibit a promising potency to treat secondary hyperparathyroidism in CKD. Diarrhea is the most common AE but it's only transient, dose-related, and mild to moderate in severity. Starting tenapanor with a low dose can be a solution for diarrhea side effect. Tenapanor doesn't cause any meaningful change in ECG, serum calcium, and other laboratory and clinical parameters. Generally, tenapanor is safe and well-tolerated in CKD patients.

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Conflict of interest

None.

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