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Redefining Phosphate Management in CKD: The Emerging Role of Tenapanor

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DESCRIPTION

Hyperphosphatemia remains a major challenge in patients with Chronic Kidney Disease (CKD) receiving maintenance hemodialysis, affecting nearly half of this population. Elevated serum phosphate is an established independent risk factor for all-cause mortality and has been strongly linked to cardiovascular morbidity, including vascular calcification and adverse cardiovascular events such as myocardial infarction and stroke [1].

Despite regular dialysis, dietary phosphate restriction, and the use of Phosphate Binders (PBs), many patients fail to achieve optimal phosphate control. PBs act by binding phosphate within the intestinal lumen, thereby reducing absorption and promoting fecal excretion. However, conventional PBs are associated with several limitations. Their substantial pill burden, often exceeding a dozen tablets per day, contributes to poor adherence and impairs quality of life. Moreover, calcium-based binders, while widely prescribed, are associated with risks of hypercalcemia, progression of vascular calcification, and increased cardiovascular events [2].

These challenges underscore the need for novel, well-tolerated therapeutic options that can effectively lower serum phosphate with a reduced treatment burden. Tenapanor, a first-in-class inhibitor of the intestinal Sodium/Hydrogen Exchanger isoform 3 (NHE3), represents a binder-free approach to phosphate management. Although initially developed for irritable bowel syndrome, tenapanor has shown promise in hyperphosphatemia management by reducing passive phosphate absorption in the gastrointestinal tract.

Recently, we conducted a systematic review and meta-analysis to provide an updated and comprehensive assessment of effectiveness and safety of tenapanor for hyperphosphatemia in hemodialysis patients [3]. Across eight short-term randomized controlled trials including 1,001 patients, tenapanor significantly reduced serum phosphate levels compared to placebo (mean difference: -1.39 mg/dL; 95% CI: -1.94, -0.84; $p<0.0001$) and nearly tripled the likelihood of achieving target phosphate levels of $\leq$ 5.5 mg/dL. Importantly, these benefits were consistent across studies but were accompanied by a higher incidence of gastrointestinal adverse events, particularly diarrhea. These findings reinforce tenapanor's potential role as an effective, binder-free therapeutic option.

The aim of this commentary is to reflect on the clinical implications of these findings, discuss tenapanor's place within the current treatment landscape, and outline directions for future research. Tenapanor was approved by the U.S. Food and Drug Administration in October 2023 for the management of hyperphosphatemia in adults with chronic kidney disease on dialysis, following robust evidence from several pivotal randomized controlled trials demonstrating its efficacy and safety. A phase 3 double-blind trial enrolling 236 patients on maintenance dialysis showed that tenapanor added to phosphate binders significantly reduced serum phosphate levels compared with placebo plus binders (-0.84 vs. -0.19 mg/dL; $P<0.001$), with only a small proportion of patients discontinuing therapy due to diarrhea (1.7%-3.4%) [4]. Similarly, another phase 3 trial assessing multiple tenapanor dosing regimens in 219 hemodialysis patients reported significant reductions in serum phosphate across all doses, with adverse effects largely limited to softened stools and mild increases in bowel movement frequency, consistent with the drug's mechanism of action [5]. Dose-dependent phosphate lowering was also confirmed in a 162-patient placebo-controlled trial, highlighting the consistent efficacy of tenapanor in diverse populations, although gastrointestinal events, particularly diarrhea, remained the most common adverse effect [6]. Supporting these individual trials, our recent meta-analysis of eight short-term RCTs including 1,001 patients further confirmed that tenapanor significantly

decreased serum phosphate and increased the likelihood of achieving target phosphate levels ≤ 5.5 mg/dL (RR: 2.80; 95% CI: 1.70-4.61), while gastrointestinal adverse events were more frequent compared with placebo [2].

Collectively, these findings indicate that tenapanor is an effective, binder-free therapeutic option for phosphate control, offering several practical advantages over conventional phosphate binders. Unlike traditional binders, which must be taken with every meal and often involve a high daily pill burden, tenapanor's twice-daily dosing and small tablet size make adherence easier and more sustainable for patients, enhancing overall convenience and quality of life. Its minimal systemic absorption reduces the risk of off-target effects, such as calcium overload or metal accumulation, that can accompany certain binders. Gastrointestinal side effects, primarily mild to moderate diarrhea, are the most frequently reported adverse events, yet they are generally manageable and lead to low discontinuation rates, contrasting with the intolerance sometimes seen with conventional therapies. Furthermore, tenapanor can be used complementarily with phosphate binders in patients with refractory hyperphosphatemia, providing additive phosphate-lowering effects while potentially reducing the binder dose. Taken together, these attributes position tenapanor as a patient-friendly, clinically advantageous option, with the potential to improve phosphate control and treatment adherence in dialysis patients, and to play an integral role in future management strategies for hyperphosphatemia.

CONCLUSION

In conclusion, hyperphosphatemia remains a significant challenge in dialysis patients, with traditional strategies limited by incomplete efficacy, high pill burden, and adverse effects. Tenapanor, a minimally absorbed, non-polymeric, calcium- and metal-free agent, offers a complementary and effective approach, both as monotherapy and alongside phosphate binders, with demonstrated reductions in serum phosphate and manageable gastrointestinal side effects. Current evidence is limited to short-term studies, highlighting the need for long-term trials to assess sustained efficacy, safety, cardiovascular outcomes, and optimal dosing strategies. Moving forward, individualized, patient-centered approaches that balance efficacy, tolerability, and adherence will be essential to optimize phosphate management and improve outcomes in this high-risk population.

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