Clinical Kidney Journal, 2025, vol. 18, no. 4, sfae383

https://doi.org/10.1093/ckj/sfae383
Advance Access Publication Date: 29 November 2024
CKJ Review

CKJ REVIEW

The efficacy and safety of RNA interference for the treatment of primary hyperoxaluria: a systematic review and meta-analysis

Huyan Yu[2,*], Hongfei Zhong[2,3,4,*], Youxia Liu[5] and Guilian Zhang[1]

[1]Department of Nephrology, Yunfu People's Hospital, Yunfu, Guangdong, People's Republic of China., [2]The Fifth Affiliated Hospital Sun Yat-Sen University, Zhuhai, Guangdong, People's Republic of China., [3]Department of Geriatrics, The Fifth Affiliated Hospital Sun Yat-Sen University, Zhuhai, Guangdong, People's Republic of China., [4]Guangdong Provincial Key Laboratory of Biomedical Imaging, The Fifth Affiliated Hospital, Sun Yat-Sen University, Zhuhai, Guangdong, People's Republic of China. and [5]Department of Nephrology, Tianjin Medical University General Hospital, Tianjin, PR China.

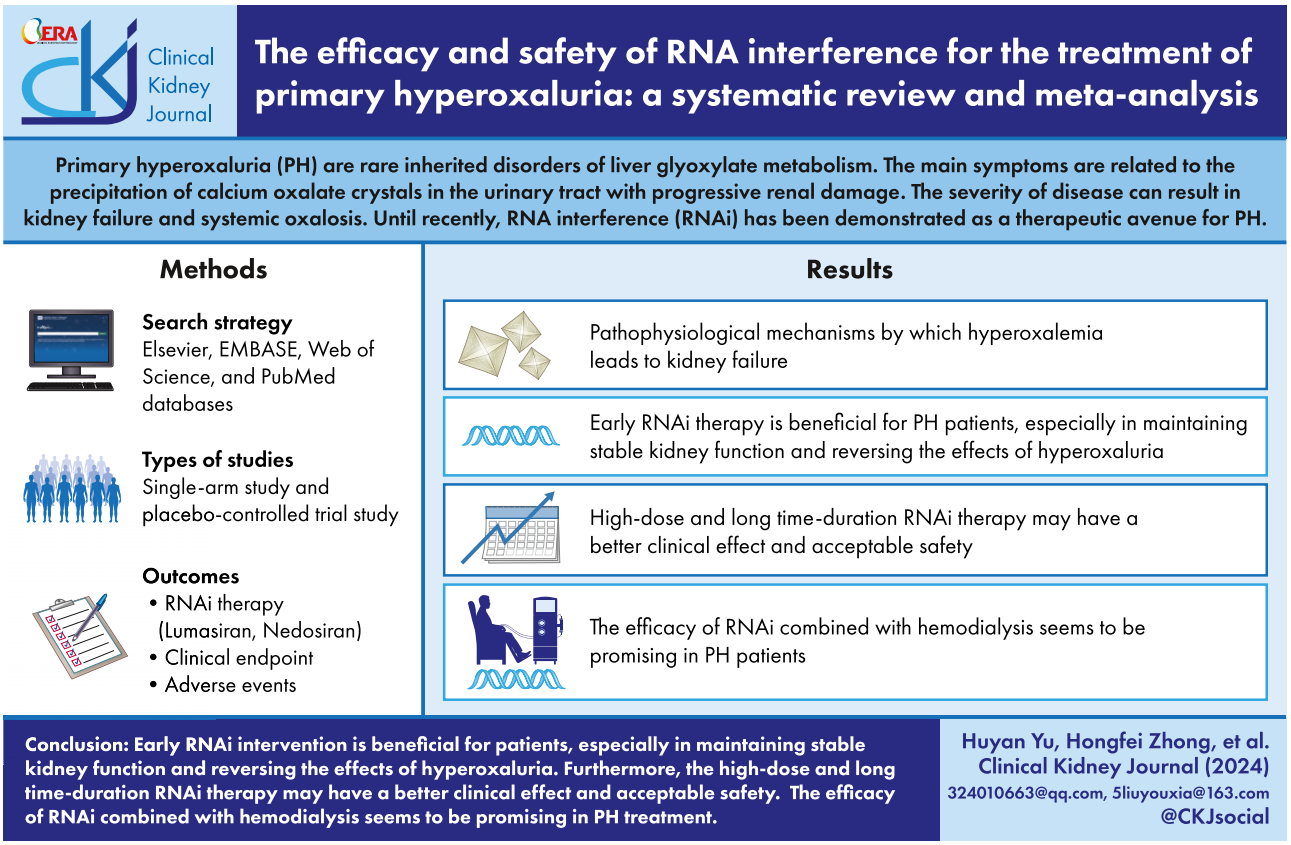
*These authors contributed equally to this work as first authors.
Correspondence to: Guilian Zhang; E-mail: 324010663@qq.com, Youxia Liu; E-mail: 5liuyouxia@163.com

ABSTRACT

Primary hyperoxaluria (PH) are rare inherited disorders of liver glyoxylate metabolism. The main symptoms are related to the precipitation of calcium oxalate crystals in the urinary tract with progressive renal damage. The severity of disease can result in kidney failure and systemic oxalosis. Until recently, RNA interference (RNAi) has been demonstrated as a therapeutic avenue for PH. We conducted a systematic review and meta-analysis to assessed the efficacy and safety of RNAi in the treatment of PH patients. The present systemic review systematically and comprehensively summarizes the pathophysiological mechanisms by which hyperoxalemia leads to kidney failure. Furthermore, we provide a detailed summary of the mechanisms of RNAi drug action in the pharmacological treatment of PH. The enrolled studies indicated that early RNAi intervention is beneficial for patients, especially in maintaining stable kidney function and reversing the effects of hyperoxaluria. Furthermore, high-dose and long time-duration RNAi therapy may have a better clinical effect. The efficacy of RNAi combined with hemodialysis seems to be promising, and it deserves more well-designed trials with large sample sizes in the future. RNAi therapy plays an important role in the treatment of PH. Early RNAi intervention is beneficial for patients, especially in maintaining stable kidney function and reversing the effects of hyperoxaluria. Furthermore, high-dose and long time-duration RNAi therapy may have a better clinical effect, and acceptable safety. The efficacy of RNAi combined with hemodialysis seems to be promising in PH treatment.

Received: 9.7.2024; Editorial decision: 14.11.2024

GRAPHICAL ABSTRACT



Keywords: Lumasiran, meta-analysis, nedosiran, placebo-controlled trial study, primary hyperoxaluria, RNA interference, single-arm study

INTRODUCTION

Primary hyperoxaluria (PH) is a rare inherited disorder of liver glyoxylate metabolism characterized by the abnormal production of endogenous oxalate, caused by mutations in the enzymes involved in endogenous oxalate synthesis, a metabolic end-product eliminated in the urine. The main symptoms are related to the precipitation of calcium oxalate crystals in the urinary tract, resulting in progressive renal damage. The severity of the disease can result in kidney failure and systemic oxalosis. Until recently, the therapies currently available for PH were either ineffective or limited, primarily focusing on supportive treatments.

PH is an autosomal-recessive inborn error of metabolism that usually manifests first as recurrent urolithiasis and/or nephrocalcinosis. PHs are underdiagnosed disorders of hepatic glyoxylate metabolism that result in excessive endogenous oxalate production. There are three types of PH (I, II and III), which correspond to three genes—glyoxylate aminotransferase (*AGXT*), glyoxylate reductase and hydroxypyruvate reductase (*GRHPR*) and 4-hydroxy-2-oxoglutarate Aldolase 1 (*HOGA1*)—which can be distinguished according to their specific enzymatic defect in glyoxylate metabolism [1–3]. Variants in any of these genes increase glyoxylate, which is oxidized to oxalate by the liver-specific peroxisomal glycolate oxidase (GO) and cytosolic lactate dehydrogenase A (LDHA).

In mammals, oxalate is primarily synthesized in the liver, and glyoxylate is considered its main precursor [4]. In human hepatocytes, glyoxylate is produced by two main pathways that occur in distinct cellular compartments: mitochondria and peroxisomes (Fig. 1). Mitochondrial glyoxylate arises from the catabolism of hydroxyproline, derived from either collagen turnover or the metabolism of animal-derived proteins [5]. HOGA1, a liver-specific enzyme, is involved in the final step of hydroxyproline metabolism and catalyzes the conversion of 4-hydroxy-2-oxoglutarate (HOG) into glyoxylate and pyruvate [6]. In mitochondria, glyoxylate can be further metabolized by the NADPH/NADH-dependent glyoxylate reductase/hydroxypyruvate reductase (GRHPR), which reduces glyoxylate and hydroxypyruvate to glycolate and D-glycerate, respectively [7–9]. GRHPR displays a dual mitochondrial and cytosolic localization and is also involved in the metabolism of cytosolic glyoxylate. In peroxisomes, glyoxylate originates either from the intake of vegetables and fruits containing glycolate, which is oxidized by GO, or from the oxidation of glycine by D-amino acid oxidase (DAO) [10]. Peroxisomal glyoxylate is metabolized by alanine:glyoxylate aminotransferase (AGXT), a pyridoxal 5′-phosphate (PLP)-dependent enzyme that catalyzes

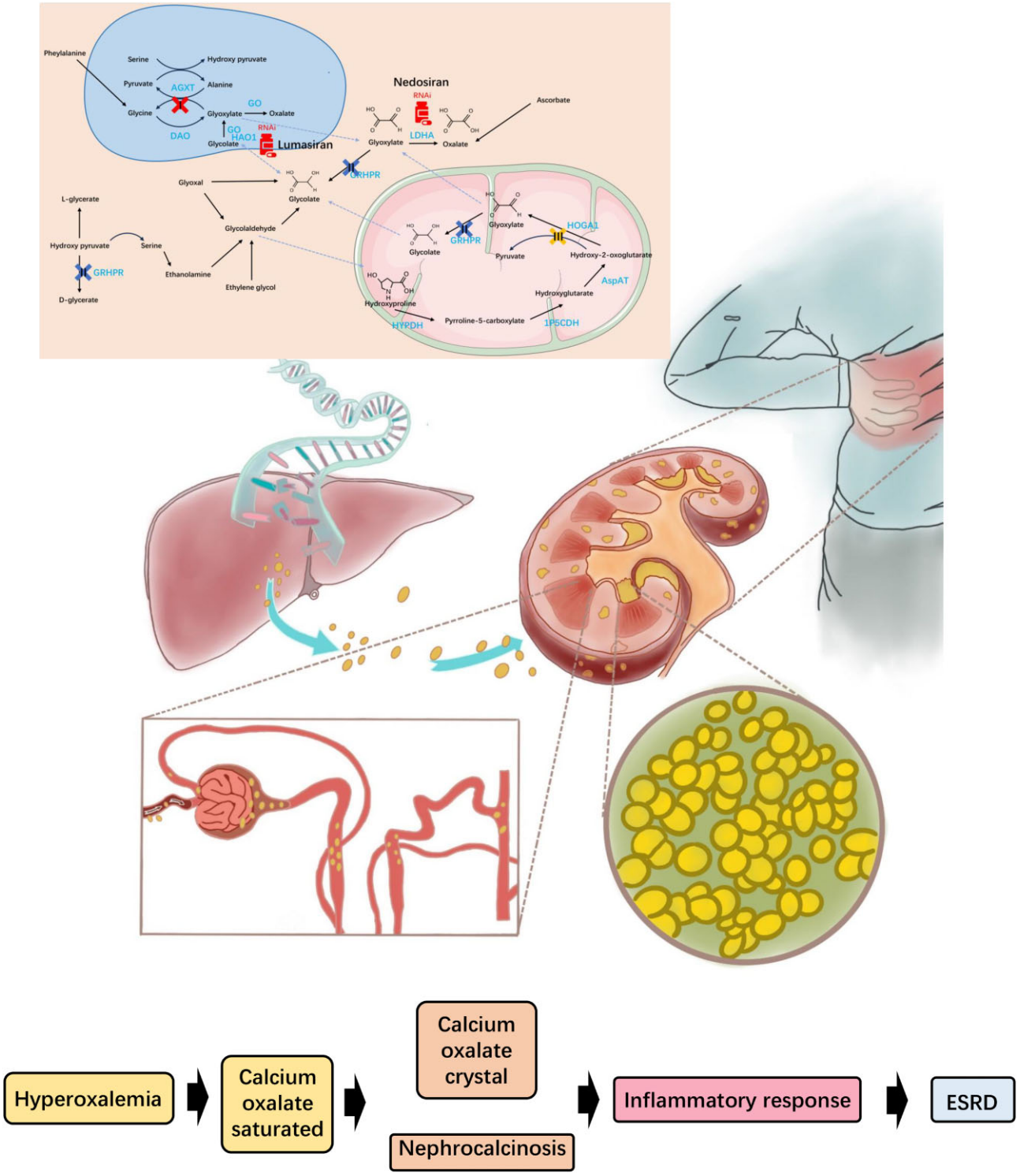


Figure 1: Molecular mechanisms leading to PH and potential RNAi therapy.

the transamination of L-alanine and glyoxylate to pyruvate and glycine, respectively. The deficiency of liver enzymes involved in glyoxylate metabolism, due to inherited mutations associated with PHs, results in the formation of large amounts of glyoxylate. Three forms of PH have been identified to date and classified as Type I (PH1), Type II (PH2) or Type III (PH3), depending on the mutated gene (Fig. 1) [11–16]. Mutations in the *AGXT* gene, which encodes human *AGT*, cause PH1 (OMIM 259900) [17]. Among the three PH types, PH1 is the most common and also the most severe. Mutations in the *GRHPR* gene, which encodes human *GRHPR*, are responsible for PH2 (OMIM 260000). Although the exact prevalence of the disease is unknown, PH2 is less common than PH1 and is generally characterized by a milder clinical presentation and the occurrence of glycolic aciduria

[18, 19]. PH3, which is caused by mutations in the *HOGA1* gene encoding human HOGA1 (OMIM 613616), accounts for approximately 10% of all PH cases. It typically exhibits a mild clinical phenotype that rarely progresses to end-stage renal disease [2, 20]. Oxalate produced within the body cannot be further metabolized and must be excreted via urine. In PH, elevated urinary oxalate levels result in calcium oxalate (CaOx) formation, which readily reaches supersaturation and precipitates due to its low solubility. Oxalate is then released from the liver and excreted through the kidneys. High concentrations of oxalate in the kidneys and urine contribute to the accumulation of CaOx in the renal tissue and tubular system, leading to urolithiasis and/or nephrocalcinosis (Fig. 1).

More recently, RNAi has been demonstrated as a therapeutic avenue for rare metabolic diseases. RNAi targeting of lactate dehydrogenase (LDH) and GO has significantly decreased oxalate synthesis [3, 21]; current RNAi therapeutics have focused on 4-hydroxyproline dehydrogenase (HYPDH), an enzyme essential in hydroxyprolinc metabolism, and GO, the enzyme responsible or glycolate to glyoxylate production. Both RNAi therapeutics, lumasiran and nedosiran, are liver specific. Lumasiran targets mRNA of the hydroxyacid oxidase 1 (*HAO1*) gene, which encodes GO, the suppression of GO prevents glycolate being converted to glyoxylate and thus oxalate; meanwhile nedosiran targets the final enzyme in the glyoxylate-to-oxalate pathway: LDHA. Thus, there was a hope that this would be an effective therapy for all types of PH. So far, relevant clinical trials have been published, but there is a lack of associated meta-analysis reports. This is the first meta-analysis and systematic review of these clinical trials.

MATERIALS AND METHODS

Search strategy

We performed a literature search in March 2024 in the Elsevier, EMBASE, Web of Science and PubMed databases. The following search terms were used: (i) “primary hyperoxaluria” or “oxalate” or “plasma oxalate”; (ii) “lumasiran” or “nedosiran” or “RNAi” or “RNA interference” or “RNA interference therapeutic”; and (iii) “single-arm trial” or “the randomized controlled trial studies.” In addition, the reference lists of retrieved papers and recent reviews were reviewed. The flow diagram of search strategy is presented in Fig. 2.

Study criteria

The inclusion criteria for studies were as follows. (i) Single-arm trial studies and the randomized controlled trial (RCT) studies providing data on the RNAi drugs (lumasiran, nedosiran) treatments (“treatment dose,” “treatment duration”); (ii) validated diagnosis of “primary hyperoxaluria” or “PH1” or PH2”; (iii) studies that provided information about the RNAi treatment (lumasiran, nedosiran) in the PH patients; and (iv) articles that reported a clear comparison of RNAi drugs treatments versus no RNAi drugs treatments population controls with a direct effect on efficacy and safety outcomes. The exclusion criteria were as follows: (i) duplicate studies; (ii) studies such as systemic reviews, meta-analyses and comments; and (iii) studies of RNAi therapy treatments without detailed research data in the clinical response.

Data extraction

Data extracted from each study included the first author’s name, the publication year, the country of study origin, clinical types of studies (single-arm study and placebo-controlled trial study), the number of patients, median age, types of PH (PH1, PH2), drug (lumasiran, nedosiran), endpoint (the response of renal function, endpoint index) and adverse events (AEs). If a study did not clearly mention any of the above key points, it had not performed the required methods. Two of the authors (H.Z. and H.Y.) independently reviewed the selected studies and extracted data. Discrepancies were resolved by discussion.

Statistical analysis

The data were abstracted and analyzed using Stata (version 12) to make the outcomes more comprehensive. The binary variable outcomes were the AEs (severe AEs, serious AEs, abdominal pain, back pain, headache, injection site erythema, muscle pain or weakness, diarrhea, injection site reaction, pyrexia and vomiting nephrolithiasis), and the data were expressed as the risk ratio (RR) with 95% confidence interval (CI), and the estimation of the effect was performed by using a random effects model. Other continuous variable outcomes were the rating scale % change from baseline in % change from baseline in plasma oxalate (PCPO), absolute change from baseline in plasma oxalate (ACPO), % change in urinary oxalate-creatinine ratio (PCUOCR), absolute change in spot urinary oxalate-creatinine ratio (ACUOCR), % change from baseline corrected for body surface area in 24-h urinary oxalate (PCUO), absolute change from baseline corrected for body surface area in 24-h urinary oxalate (ACUO), absolute change in 24-h urinary oxalate excretion (ACUOE), 24-h urine oxalate:creatinine ratio (UOCR) and plasma oxalate (PO). Data was expressed as the standardized mean difference (SMD) with 95% CI. The endpoint outcome of the continuous data was presented as the effect-size (ES) (median, 95% CI) in the single-arm studies. When combining studies, the random effects model was used to account for study heterogeneity. We first conducted heterogeneity tests for each indicator, based on the methodologies of the included articles and intervention studies [22]. Heterogeneity-related tests also indicated the need to improve subgroup analysis, which led us to perform subgroup analyses. The subgroup analyses were primarily based on the type of RNAi drugs (nedosiran and lumasiran) in the included RCTs and single-arm studies, as well as drug dosage and treatment duration. We used Q statistic and I^2 tests to evaluate the heterogeneity. Low, moderate and high heterogeneities were represented by thresholds of $<25\%$, 25%–75% and $>75\%$, respectively. $P \leq .05$ was considered significant in all statistical tests.

Data analysis

The binary variable outcomes were the incidence of AEs (severe AEs, serious AEs, abdominal pain, back pain, headache, injection site erythema, muscle pain or weakness, diarrhea, injection site reaction, pyrexia and vomiting nephrolithiasis). In addition, the data for endpoint index (PCPO, ACPO, PCUOCR, ACUOCR, PCUO, ACUO, ACUOE) were expressed as SMD with 95% CI; the estimation of the effect was performed by using a random effects model. A total of 15 studies were included in this article, with 4 single-arm studies, 4 placebo-controlled trial studies [23–30] and 7 case reports [31–37] (Table 4) included in the quality systematic review after 423 registered studies were assessed. Eight articles with a total of PH patients were included in the single-arm

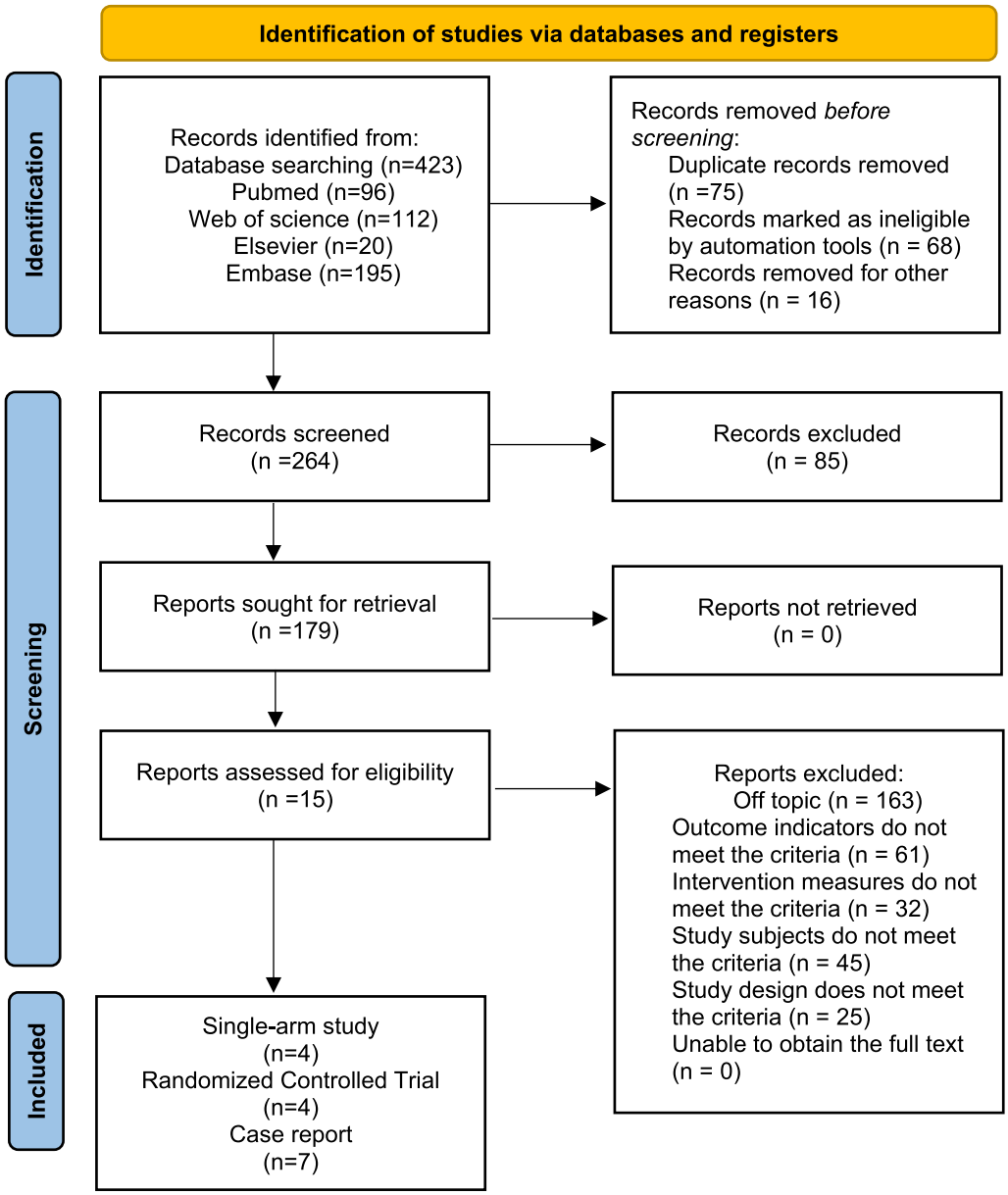


Figure 2: Flow diagram for the search strategy.

and placebo-controlled trial studies (Table 1), and the efficacy and safety of RNAi (lumasiran, nedosiran) in PH patients were examined. The type of the study (single-arm study or placebo-controlled trial), the outcomes of the endpoint (primary and secondary endpoint) (Table 2) and AEs after treatment with RNAi drugs in PH patients were reported (Table 3).

Study quality and risk of bias assessment

We conducted a thorough evaluation of study quality and risk of bias. Specifically, we employed the RoB 2.0 tool [38] for RCTs and the Newcastle–Ottawa Scale [39] for single-arm studies. Studies will be reviewed and scored as "high risk," "low risk" or "unclear" in each of the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Inter-rater reliability of the RoB tool has been demonstrated to range from fair to substantial depending on the assessment domain. The results of the risk of bias assessment will be summarized narratively with full assessments included in the Supplementary data. Risk of bias between studies will be assessed [40] and presented as funnel plots and Egger tests [41]. The detailed assessments are provided in the Supplementary data.

RESULTS

Efficacy and safety of RNAi for the treatment of PH on the placebo-controlled trial studies

Efficacy

Four placebo-controlled trial studies were included in the meta-analysis; all studies included in the analysis reported the efficacy

Table 1: Baseline characteristics of included studies: single-arm and placebo-controlled trial studies.

			Participants					Therapy			Endpoint		
Author/year	Country	Clinical types of RCTs	Number	Median age (years)	Female (%)	Types of PH	eGFR Median (range)/mean (SD)	Drug	Dose (mg/kg)	Duration	Response of renal function/eGFR	Main endpoint index	AEs
Hoppe 2022 [22]	USA	Single-arm study	18	23.8	50	PH1/PH2	82.16 (26.493)	Nedosiran	1.5–6	52 weeks	NR	PCUO	√
Sas 2021 [23]	USA	Single-arm study	18	4.2	56	PH1	111 (65–174)	Lumasiran	3–6	6 months	eGFR remained stable	PCPO, ACPO, PCUOCR, ACUOCR	√
Goldfarb 2023 [24]	USA	Placebo-controlled trial study	4	44.8	50	PH3	89 (34)	Nedosiran	3	85 days	NR	ACUOE, PCPO	√
Baum 2022 [25]	Japan	Placebo-controlled trial study	35	23.7	52.2	PH1	19 (82.6)	Nedosiran	2.7–3.4	6 months	No significant change	ACUOE, PCPO	√
Michael 2022 [26]	USA	Single-arm study	21	8	43	PH1	16.5 (8.6–34.1)	Lumasiran	3–6	6 months	eGFR decreased 17%	PCPO, ACPO, PCUOCR, ACUOCR	√
Hulton 2022 [27]	USA	Placebo-controlled trial study	39	14	33	PH1	81.6 (26.8)	Lumasiran	3	6 months	eGFR remained stable	PO, PCPO, PCUOCR	√
Hayes 2022 [28]	USA	Single-arm study	18	16.3	NR	PH1	111 (65–174)	Lumasiran	3–6	12 months	eGFR remained stable	PCPO, ACPO, PCUOCR, ACUOCR, PCUO, ACUO	√
Frishberg 2021 [29]	UK	Placebo-controlled trial study	20	15	65	PH1	78 (21)	Lumasiran	0.3–6	3–6 months	Kidney function improved	ACUOE, PO, PCUOCR	√

HD, hemodialysis; NR, not reported; SD, standard deviation.

Table 2: Endpoint of RNAi for the treatment of PH.

		Results		
Endpoint		SMD/ES	95% CI	I^2 (%)
Placebo-controlled trial study				
ACUOE (mg/mg)				
		−1.88	−2.63, −1.14	81.8
Drug	Lumasiran	−3.86	−5.51, −2.56	70.4
	Nedosiran	−0.90	−1.81, 0.02	84.4
Dose	1 mg/qm	−2.6	−4.12, −1.08	69.8
	3 mg/qm	−1.48	−2.34, −0.62	85.6
	3 mg/q3m	−11.66	−18.22, −5.11	24.8
Duration	1 months	−2.84	−4.03, −1.64	62.3
	3 months	−3.04	−4.33, −1.75	81.7
	6 months	0.83	−0.58, 2.25	
PCUO				
		3.37	2.80, 3.95	84.5
Drug	Lumasiran	3.62	2.98, 4.26	90.4
	Nedosiran	2.44	1.19, 3.69	77.1
Dose	3 mg/qm	3.37	2.80, 3.95	84.5
Duration	1 months	2.61	1.72, 3.50	
	3 months	3.15	2.26, 4.04	82.0
	6 months	5.73	4.36, 7.11	85.0
UOCR				
		−2.77	−3.24, −2.30	77.9
Drug	Lumasiran	−2.77	−3.24, −2.30	77.9
Dose	1 mg/qm	−1.97	−3.12, −0.83	0
	3 mg/qm	−3.03	−3.58, −2.49	86.3
	3 mg/q3m	−2.13	−3.67, −0.58	69.3
Duration	1 months	−1.99	−2.65, −1.33	70.3
	3 months	−3.04	−3.81, −2.28	56.9
	6 months	−5.35	−6.74, −3.96	
PO (μmol/L)				
		−1.71	−2.11, −1.30	30.1
Drug	Lumasiran	−1.71	−2.11, −1.30	30.1
Dose	1 mg/qm	−0.72	−2.18, 0.74	19.6
	3 mg/qm	−1.86	−2.29, −1.42	18.1
	3 mg/q3m	−0.39	−2.38, 1.61	
Duration	1 months	−1.37	−1.99, −0.74	19.0
	3 months	−1.64	−2.32, −0.95	2.6
	6 months	−2.49	−3.36, −1.61	
Single-arm study				
PCPO				
		37.74	30.57, 44.92	97.4
Drug	Lumasiran	37.74	30.57, 44.92	97.4
Dose	3 mg	40.63	33.57, 47.69	36.4
	6 mg	36.98	26.42, 47.55	98.5
Duration	6 months	35.14	28.34, 41.94	95.6
	12 months	47.14	45.02, 49.26	
Hemodialysis	Yes	42.04	28.96, 55.13	72.4
	No	35.42	28.01, 42.82	97
ACPO				
		−19.85	27.10, 12.61	99.8
Drug	Lumasiran	−19.85	27.10, 12.61	99.8
Dose	3 mg	−42.33	54.66, 30.00	93.7
	6 mg	−5.80	−6.97, −4.63	94
Duration	6 months	−23.26	−33.50, −13.02	99.9
	12 months	−7.30	−7.99, −6.61	
Hemodialysis	Yes	−21.34	−49.17, 6.49	98.9
	No	−19.42	−30.93, −7.92	99.9

Table 2: Continued

Endpoint		Results		
		SMD/ES	95% CI	I^2 (%)
PCUOCR				
		66.78	62.38, 71.19	95.7
Drug	Lumasiran	66.78	62.38, 71.19	95.7
Dose	3 mg	39.5	31.98, 47.02	
	6 mg	71.89	71.07, 72.70	0
Duration	6 months	63.40	56.41, 70.38	97.1
	12 months	71.90	70.42, 73.38	
Hemodialysis	Yes	55.92	24.17, 87.67	98.5
	No	71.88	70.91, 72.86	0
ACUOCR				
		−0.41	−0.61, −0.22	99.8
Drug	Lumasiran	−0.41	−0.61, −0.22	99.8
Dose	3 mg	−0.19	−0.20, −0.18	
	6 mg	−0.49	−0.49, −0.49	0
Duration	6 months	−0.39	−0.62, −0.16	99.9
	12 months	−0.49	−0.44, −0.54	–
Hemodialysis	Yes	−0.34	−0.63, −0.04	99.3
	No	−0.49	−0.49, −0.49	0
PCUO				
		49.36	26.46, 72.25	99.2
Drug	Lumasiran	47.53	19.87, 75.18	99.4
	Nedosiran	55.00	45.85, 64.15	
Dose	3 mg	32.64	−10.87, 76.15	98.5
	6 mg	65.93	60.86, 71.00	82.7
Duration	6 months	39.56	−17.10, 96.21	99.7
	12 months	60.26	52.52, 68.01	63.6
Hemodialysis	Yes	36.96	−14.62, 88.54	99.6
	No	62.45	49.39, 75.51	86.9
ACUO				
		−1.23	1.19, 1.26	99.3
Durg	Lumasiran	−1.23	1.19, 1.26	99.3
Dose	3 mg	−0.53	0.44, 0.62	
	6 mg	−1.34	1.31, 1.38	58.4
Duration	6 months	−1.23	1.19, 1.26	99.6
	12 months	−1.24	1.11, 1.37	
Hemodialysis	Yes	−0.74	0.67, 0.82	98.7
	No	−1.35	1.31, 1.39	

response of RNAi (lumasiran, nedosiran) for the treatment of PH patients, where the endpoint included ACUOE, PCUO, UOCR and PO. We used the SMD to reduce the complexity regarding the sources of the endpoint index. In the meta-analysis, a significant change was found in those four indicators (ACUOE: SMD = −1.88, 95% CI −2.63 to −1.14, I^2 = 81.8%; PCUO: SMD = 3.37, 95% CI 2.80 to 3.95, I^2 = 84.5%; UOCR: SMD = −2.77, 95% CI −3.24 to −2.30, I^2 = 77.9%; PO: SMD = −1.71, 95% CI −2.11 to −1.30, I^2 = 30.1%). Due to the heterogeneity, we also considered the subgroup analysis. The subgroup analysis of endpoint included drug, dose and treatment duration. In the subgroup analysis of drugs in ACUOE, a significant SMD of −3.86 (95% CI −5.51 to −2.56, I^2 = 70.4%) was found for lumasiran compared with nedosiran (SMD = −0.90, 95% CI −1.81 to 0.02, I^2 = 84.4%) in ACUOE. Furthermore, the index of PCUO also had the same tendency (lumasiran: SMD = 3.62, 95% CI 2.98 to 4.26, I^2 = 90.4% versus nedosiran: SMD = 2.44, 95% CI 1.19 to 33.69, I^2 = 77.1%). In addition, a dose–response relationship was observed in the subgroup of drug dose and treatment duration (Fig. 2) in the decrease of 24-h urine oxalate:creatinine ratio: dose response 1 mg monthly (mg/qm), SMD = −1.97 (95% CI −3.12 to −0.83, I^2 = 0%); 3 mg/qm, SMD = −1.97 (95% CI −3.12 to −0.83, I^2 = 0%); and treatment duration 1 month, SMD = −1.99 (95% CI −2.65 to −1.33, I^2 = 70.3%), 3 months, SMD = −3.04 (95% CI −3.81 to −2.28, I^2 = 56.9%) and 6 months SMD = −5.35 (95% CI −6.74 to −3.96). Moreover, PO also had a similar dose response: dose response 1 mg/qm: SMD = −0.72 (95% CI −2.18 to 0.74, I^2 = 19.6%); 3 mg/qm, SMD = −1.86 (95% CI −1.99 to −0.74, I^2 = 18.1%); treatment duration 1 month, SMD = −1.37 (95% CI −2.65 to −1.33, I^2 = 19.0%), 3 months SMD = −1.64 (95% CI −2.32 to −0.95, I^2 = 2.6%) and 6 months SMD = −2.49 (95% CI −3.36 to −1.61). There was no significant heterogeneity after subgroup analysis in PO.

Safety

We investigated all types of AEs. A total of six subjects were included in the placebo-controlled trial study (abdominal pain, back pain, headache, injection site erythema, muscle pain or

Table 3: AEs of RNAi for the treatment of PH.

AEs		Results			
		RR/ES	95% CI	I^2 (%)	Risk
Placebo-controlled trial study (RR, 95% CI)					
Serious AEs		0.41	0.10, 1.60	0	
Abdominal pain		1.35	0.39, 4.68	53.2	
Back pain		0.58	0.13, 2.48	62.7	
Headache		1.08	0.33, 3.53	0	
Injection site erythema		1.19	0.57, 2.50	0	
Muscle pain or weakness		3.00	0.21, 43.66	0	High
Nephrolithiasis		0.30	0.07, 1.24	0	
Single-arm study (ES, 95% CI)					
Severe AEs		0.200	−0.002, 0.402		
Serious AEs					
Hemodialysis	Yes	0.167	−0.132, 0.465		
	No	0.333	0.095, 0.572		
Diarrhea					
Drug	Nedosiran	0.153	−0.048, 0.355	0	
	Lumasiran	0.133	−0.039, 0.305		
Dose	3 mg/kg	0.13	−0.007, 0.268	0	
	6 mg/kg	0.25	−0.174, 0.674		
Duration	6 months	0.133	−0.039, 0.305	0	
	12 months	0.153	−0.048, 0.355	0	
Hemodialysis	Yes				
	No	0.142	0.011, 0.273	0	
Injection site reaction					
Drug	Nedosiran	0.167	−0.132, 0.465		
	Lumasiran	0.193	0.078, 0.307	0	
Dose	1.5 mg/kg	0.167	−0.132, 0.465		
	3 mg/kg	0.231	0.052, 0.410	0	
	6 mg/kg	0.167	0.018, 0.316	0	
Duration	6 months	0.167	−0.132, 0.465		
	12 months	0.193	0.078, 0.307	0	
Hemodialysis	Yes	0.167	−0.132, 0.465		
	No	0.193	0.078, 0.307	0	
Pyrexia					
Drug	Lumasiran	0.341	0.216, 0.466	0	High
Dose	3 mg/kg	0.369	0.157, 0.580	28.2	High
	6 mg/kg	0.333	0.145, 0.522	0	High
Duration	6 months	0.341	0.216, 0.466	0	High
Hemodialysis	Yes	0.167	−0.132, 0.465		
	No	0.378	0.240, 0.516	0	High
Vomiting					
Drug	Nedosiran	0.153	−0.048, 0.355	0	
	Lumasiran	0.126	0.037, 0.215	0	
Dose	3 mg/kg	0.108	0.008, 0.208	0	
	6 mg/kg	0.176	0.035, 0.316	0	
Duration	6 months	0.126	0.037, 0.215	0	
	12 months	0.153	−0.048, 0.355	0	
Hemodialysis	Yes	0.167	−0.132, 0.465		
	No	0.128	0.043, 0.212	0	

weakness, and nephrolithiasis), as shown in Table 3. Due to the limited data, we have not investigated the subgroup analysis. Among the six AE categories, muscle pain or weakness had a high risk (RR = 3.00, 95% CI 0.21 to 43.66, $I^2 = 0\%$), but not statistical significance. Meanwhile, the other AEs (abdominal pain, back pain, headache, injection site erythema and nephrolithiasis) had no bad effects.

Efficacy and safety of RNAi for the treatment of PH on the single-arm studies

Efficacy

Four single-arm studies were included in the meta-analysis, where the endpoint included PCPO, ACPO, PCUOCR, ACUOCR, PCUO and ACUO. The endpoint outcome of the continuous data

was presented as the ES (median, 95% CI). The random-effects model was used because of significant heterogeneity. Percent change from baseline in PO. In the meta-analysis, significant change was found in those six indicators (PCPO: ES = 37.74, 95% CI 30.57 to 44.92, I^2 = 97.4%; ACPO: ES = −19.85, 95% CI −27.10 to −12.61, I^2 = 99.8%; PCUOCR: ES = 66.78, 95% CI 62.38 to 71.19, I^2 = 95.7%; ACUOCR: ES = −0.41, 95% CI 0.22 to 0.61, I^2 = 99.8%; PCUO: ES = 49.36, 95% CI 26.46 to 72.25, I^2 = 99.2%).

Safety

A total of six subjects were included in the placebo-controlled trial study (severe AEs, serious AEs, diarrhea, injection site reaction, pyrexia and vomiting), as shown in Table 3. The subgroup analysis of any AEs included drug, dose, treatment duration, and hemodialysis or not. Among the six AEs categories, pyrexia had a high risk (ES = 34.1%, 95% CI 0.21 to 0.46, I^2 = 0%). In the subgroup analysis, patients not undergoing hemodialysis had a higher risk of AEs [injection site reaction (ES: 0.167 vs 0.193), pyrexia (ES: 0.167 vs 0.378)]. Furthermore, the risk of diarrhea and vomiting have a dose–response relationship, high-dose drug medication may present a higher risk of the AEs, and drug treatment duration has the same tendency (for diarrhea, injection site reaction and vomiting).

The involved case report of RNAi therapy in PH

A total of seven case reports were included in this article, and the details are shown in Table 4. Twelve patients were fully discussed. We discuss the full spectrum of participant clinical features, therapeutic schedule and clinical efficacy [laboratory indexes: PO, urinary oxalate concentration, estimated glomerular filtration rate (eGFR); imaging indexes: were included]. Matthew and Anne-Laure *et al*. reported that in patients who underwent kidney-only transplantation, undergoing RNAi therapy (lumasiran and nedosiran) had a curative effect, such as no evidence of tissue oxalate crystal deposition, and sufficient decrease of PO. This drug targets the hepatic overproduction of oxalate, making kidney-only transplantation a potentially practical novel approach for managing PH1 patients with advanced kidney disease. Two studies have reported on young infant patients receiving medical therapy alone, and the treatment in Taroni *et al*. was more aggressive—these authors describe the effect of lumasiran initiated at 10 days of life in a newborn with prenatally diagnosed PH1 based on family history and genetic testing, which is the first late-preterm baby treated with lumasiran at birth, with a 20-month follow-up. The use of lumasiran appears to be safe in this type of patient. Early clinical intervention of newborns with antenatal diagnosis of PH1 represents a therapeutic innovation.

DISCUSSION

We systematically and comprehensively summarize the pathophysiological mechanisms by which hyperoxalemia leads to kidney failure. Furthermore, we provide a detailed summary of the mechanisms of RNAi drug action in the pharmacological treatment of PH, which is shown in Fig. 1. RNAi drugs (lumasiran, nedosiran) are a newly emerging treatment for PH. In recent years, scholars have begun to conduct related placebo-controlled trial studies and single-arm clinical trials (Frishberg *et al*. [29], Sally *et al*. [27] and Hayes *et al*. [28]). In recent years, there have been updated comprehensive studies in the RNAi treatment of PH, but there has ben no comprehensive summary and review to date. Hence, updating related meta-analysis research is necessary.

To the best of our knowledge, this was the first meta-analysis to fully assess the efficacy and safety of RNAi in the treatment of PH patients. Single-arm studies and placebo-controlled trial studies were involved in this meta-analysis; we evaluated both the efficacy index (PCPO, ACPO, PCUOR, ACUOCR, PCUO, ACUO, ACUOE) and safety index (severe AEs, serious AEs, abdominal pain, back pain, headache, injection site erythema, muscle pain or weakness, diarrhea, injection site reaction, pyrexia and vomiting nephrolithiasis) in the treatment of PH patients. Furthermore, we undertook a subgroup assessment (drug, duration, dose and hemodialysis). In this systematic review, we found that the available evidence provides some support for the efficacy of RNAi drugs (especially lumasiran), having an ideal therapeutic effect to improve multiple endpoints in PH patients.

In the involved RCTs, ACUOE and PCUO are commonly used to assess the impact of medications or treatments on urinary oxalate excretion. These metrics are often used together to comprehensively assess the impact of treatments on urinary oxalate excretion. In this meta-analysis, treatment with lumasiran was shown to achieve substantial and sustained reductions in urinary oxalate compared with nedosiran. Lumasiran is a small interfering RNA (siRNA) that targets and inhibits the expression of the *HAO1* gene in the liver. *HAO1* encodes GO, an enzyme that plays a crucial role in oxalate production. By inhibiting GO production, lumasiran can significantly reduce the generation of oxalate in the body, thereby reducing urinary oxalate excretion [42]. Meanwhile, nedosiran is also an siRNA that targets another key enzyme in oxalate metabolism LDH. It reduces oxalate production by inhibiting LDH expression [43]. In contrast to nedosiran, lumasiran directly inhibits the key enzyme GO in oxalate production, and may have higher specificity and targeting accuracy, thus showing better efficacy in reducing oxalate production and excretion [44]; this may explain the results we obtained. This rapid response demonstrates the effectiveness of lumasiran in inhibiting oxalate production. Similarly, in a phase 3 clinical trial, we found that lumasiran significantly reduced urinary oxalate levels in patients with PH1. The trial results showed that, at the third month, the median urinary oxalate levels in the lumasiran group decreased by 65% [24]. ACUOE demonstrated a dose–response relationship, with the 3 mg every 3 months (q3m) regimen yielding the best efficacy and exhibiting the lowest heterogeneity (24.8%). Furthermore, ACUOE also demonstrated a duration-dependent pharmacodynamic response relationship; while in the PCUO index, long-term and appropriate and reasonable high-dose RNAi therapy has acceptable efficacy. Lumasiran has demonstrated significant efficacy in reducing 24-h urinary oxalate excretion, though no clear dose–response relationship was observed. Among the dosing regimens, the 3 mg/q3m regimen outperformed other doses, suggesting that a lower frequency with an appropriate dose may be more effective. However, the 6-month treatment results were relatively suboptimal, indicating that adjustments to the dosing regimen may be needed over longer treatment periods to maintain optimal efficacy. Regarding percentage changes from baseline in 24-h urinary oxalate excretion, lumasiran also showed superior results, with a clear time–response relationship observed, meaning that the reduction in urinary oxalate increased over time. Additionally, changes in the 24-h urine oxalate:creatinine ratio exhibited both time–response and dose–response relationships, indicating that the treatment effects improved as time progressed and with dose adjustments. These findings suggest that close monitoring of patients and dose modifications are essential to achieve

Table 4: The case report involved in this study.

	Participant						Treatment				
Author/year	Number	Gender	Age	Diagnosis	Family history	Genetic testing	HD	Transplant	RNAi	Therapeutic schedule	Efficacy
Taroni 2024 [30]	1	Female	10 days	PH1	Yes	c.466G>A-p.(Gly156Arg)-c.943–1G>T	No	No	Lumasiran	Lumasiran 3 mg/kg qm (until 10 kg) then 6 mg/kg q3m	Urinary oxalate↓ PO↓
Breeggemann 2023 [31]	1	Male	19 years	PH1	No	c.973delG, exon 10 + c.836T>C, exon 8	HD was initiated at a frequency of 6 days	Kidney transplant	Nedosiran	Nedosiran on POD 6 and discharged on POD 10	PO↓ No evidence of tissue oxalate crystal deposition Lower tissue oxalate stores
Breeggemann 2023 [32]	5	Femal/Male	Patient 1: 1.5 years Patient 2: 17 years Patient 3: 6 years Patient 4: 8 years Patient 5: 8 years	PH1	No	Patient 1: c.731T>C Patient 2: c.[508G>A];[847–1G>C] Patient 3: c.[33del];[731T>C] Patient 4: c.[33dup];[847–11G>C] Patient 5: c.[33del];[454T>A]	No	Kidney transplant	Lumasiran	13 months on lumasiran therapy	PO↓ Kidney function recovered partially
Chiodini 2022 [33]	1	Male	28 years	PH1	No	Entire exon 9 on the *AGXT* gene	No	No	Lumasiran	Lumasiran qm then q3m	UOCR↓ PO eGFR remained stable No new kidney stones
Méaux 2022 [34]	3	Male	Patient 1: 9 days Patient 2: 2.5 months	PH1	No	Patient 1: *AGXT* gene (c.33dup and c.321_344del) Patient 2: homozygous c.731 T>C (p.Ile244Thr) variant	No	No	Lumasiran	Monthly lumasiran (3 times at 6 mg/kg, then 3 mg/kg)	Urinary oxalate↓ Substantial improvement in kidney function

Table 4: Continued

Author/year	Participant						Treatment				
	Number	Gender	Age	Diagnosis	Family history	Genetic testing	HD	Transplant	RNAi	Therapeutic schedule	Efficacy
			Patient 3: 3 months			Patient 3: homozygous c.731 T>C (p.Ile244Thr) variant					
Poyah 2021 [35]	1	Female	40 years	PH1	No	(AGXT c.680 + 1G>A)	14 months of high-intensity dialysis	No	Lumasiran	Lumasiran 1 mg/kg qm 3 months	No signs of renal recovery Extra-renal involvement
Shee 2021 [36]	1	Female	17 years	PH1	No	AGXT mutation (c.973delG, exon 10)	HD	No	Nedosiran	Monthly abdominal subcutaneous injection at dose of 1.5 mg/kg	PO↓ No AEs, temporary injection site discomfort

HD, hemodialysis; POD, oral administration drug.

the best clinical outcomes. We evaluate the effects of different dosing regimens on PO levels in patients with PH1. A noticeable time-dependent follow-up effect was observed, with therapeutic outcomes improving as the duration of medication use increased. Specifically, significant reductions in PO levels were noted over 1, 3 and 6 months, indicating that prolonged treatment enhances overall effectiveness. However, the results for the 3 mgq3m dosing regimen did not align with the expected trend. The data showed less significant reduction in PO levels compared with the 1 mg monthly (1 mg/qm) and 3 mg monthly (3 mg/qm) regimens. This discrepancy may be attributed to the limited amount of data available for the 3 mgq3m group. The small sample size in this group might have contributed to the variability and the less reliable outcomes. During the 6-month primary analysis period, lumasiran significantly reduced both PO and urinary oxalate levels in patients with impaired kidney function, and it was generally well tolerated. The most common AE related to lumasiran was injection-site reactions, all of which were mild and transient, ensuring good patient adherence to treatment. These findings indicate that lumasiran is an effective treatment option, particularly for patients with impaired kidney function. However, since its efficacy is significantly influenced by both time and dosage, treatment regimens need to be carefully optimized according to individual patient needs to ensure long-term effectiveness and quality of life improvement. Furthermore, this study provides valuable insights for developing personalized treatment strategies, helping clinicians make more informed decisions regarding dosage, treatment cycles and monitoring frequency.

These findings have significant clinical implications. Firstly, the significant reduction in urinary oxalate over extended treatment periods indicates that prolonged therapy can enhance drug efficacy. This supports the idea of continuous and long-term medication use for PH1 patients to achieve the best outcomes. Secondly, the comparison of different dosing groups shows a clear dose–response relationship. The higher dose (3 mg/qm) results in more significant therapeutic effects than the lower dose (1 mg/qm), suggesting that clinicians should consider higher doses to achieve better outcomes. At the same time, the effectiveness of the 3 mg/q3m dosing, though significant, is less than that of the monthly dosing, emphasizing the impact of dosing frequency on efficacy.

The involved RCTs underscore the importance of prolonged treatment and appropriate dosing regimens in managing PH1. Lumasiran has demonstrated superior efficacy in reducing urinary and PO levels, with higher doses and more frequent administration leading to better outcomes; the 3 mg/qm dosing regimen appears to provide the most optimal therapeutic efficacy. However, additional research with larger sample sizes is necessary to fully elucidate the long-term effects and optimize treatment strategies for PH1 patients.

In the singe-arm studies, the analysis of lumasiran treatment efficacy on various outcome measures demonstrates significant differences in therapeutic response, particularly between patients undergoing dialysis and those who are not. These findings provide crucial clinical insights for the management of PH1. For PCPO and ACPO, no significant dose–response relationships were observed, indicating that changes in dose did not significantly impact reductions in PO levels. However, among patients receiving dialysis, these measures showed more substantial improvements, suggesting that dialysis plays an important supportive role in the oxalate clearance process. This effect appears to complement the pharmacological action of lumasiran, possibly enhancing the reduction in PO levels. Moreover, the 3 mg dose was found to be more effective across these parameters compared with other doses, indicating that this dosing regimen may yield more significant clinical benefits. For PCUOCR and ACUOCR, a clear dose–response and time-response relationship was observed, indicating that increased dose and prolonged treatment duration resulted in greater reductions in UOCR. The data indicate that higher doses and extended treatment durations positively influenced these measures, suggesting that increased treatment intensity and prolonged treatment courses can more effectively reduce urinary oxalate levels.

Lumasiran has demonstrated the ability to significantly and consistently reduce PO and urinary oxalate levels over extended treatment periods, particularly in dialysis patients. This highlights the importance of prolonged therapy to achieve optimal treatment outcomes. Therefore, continuous and long-term treatment with lumasiran is recommended for PH1 patients, especially those undergoing dialysis, to maximize clinical benefits. Second, the 3 mg dosing regimen was found to be the most effective for most outcome measures, indicating that higher doses may yield better efficacy. Thus, increasing the dosage might be a beneficial strategy to enhance the therapeutic effects of lumasiran. For instance, increasing the dosage, modifying the administration frequency or synchronizing lumasiran administration with dialysis schedules might help optimize treatment efficacy and better reduce oxalate burden. Further research involving larger sample sizes, especially in dialysis populations, is essential to clarify the long-term effects of lumasiran and develop appropriate treatment protocols for these patients.

Overall, the dose and duration treatment effects in single-arm studies are consistent with the findings in RCTs. The changes of PO and urine oxalate in patients undergoing hemodialysis were on the contrary after the RNAi usage; furthermore, the treatment has a better clinical efficacy for decreasing PO in PH patients.

The profound lowering of PO and UOCR, and significant decrease in the 24-h urinary oxalate excretion in both the single-arm clinical trials and placebo-controlled trial studies, may lead to improvements in clinical outcomes, such as kidney stone events, nephrocalcinosis and renal function. The 24-h urinary oxalate excretion is an accepted surrogate marker of PH disease burden and long-term risk for renal failure [45, 46]. In previous studies, treatment with lumasiran was shown to achieve substantial and sustained reductions in urinary oxalate in patients with relatively preserved renal function [47]. Furthermore, the subgroup analysis of placebo-controlled trial studies suggest that the 3 mg/qm (3 mg/kg once monthly dose) regimen appeared to lead to more rapid and higher-magnitude reduction of UOCR relative to 1 mg/qm (1 mg/kg once monthly), and the 3 mg/qm regimen may significantly prolong 24-h urinary oxalate excretion compared with 1 mg/qm. These results may be consistent with evidence that chemically stabilized siRNA molecules, such as lumasiran, slowly release the functional siRNA into the RNAi pathway over time [48].

The majority of lumasiran-related AEs in this meta-analysis consisted of injection-site reactions, and no serious or severe AEs were considered lumasiran related, which is consistent with what was previously reported in patients with preserved renal function [47]. Meanwhile, for the dose–response relationship of single-arm clinical trials, the subgroup analysis presented the same tendency: PCUCR (3 mg/qm versus 6 mg/qm), ACUCR (3 mg/qm versus 6 mg/qm), PCUO (3 mg/qm versus 6 mg/qm) and ACUO (3 mg versus 6 mg). In summary, as discussed above, long-term and appropriate and reasonable high dose of RNAi

therapy indeed has acceptable efficacy and safety. It is worth considerating that most of the studies involved were lumasiran clinical trials; more studies are required to detect any long-term differences between nedosiran and lumasiran regarding sustained effects on urinary oxalate and PO, and AEs. A proportion of patients in the single-arm studies were on hemodialysis, and in the hemodialysis subgroup, the efficacy of RNAi therapy (lumasiran and nedosiran) combined with early hemodialysis was found to be significantly enhanced. In the single-arm clinical trials, we also discussed the AEs during RNAi treatment and found that the risk of suffering from AEs, such as diarrhea, injection site reaction and vomiting, increased with the dose, and duration of medication presented the same tendency. Meanwhile, in the hemodialysis subgroup, we found that there may be a lower risk of suffering AEs after hemodialysis—the oxalate-related metabolism may decrease significantly, and AEs are relatively reduced. In summary, RNAi therapy medication demonstrates enhanced efficacy and safety when administered after hemodialysis. As discussed above, the mechanism of action of lumasiran involves targeting and degrading the specific RNA responsible for oxalate production, thereby reducing the amount of oxalate formed in the body. PH1 leads to the accumulation of high levels of oxalate in the urine and blood, increasing the risk of kidney stones and renal failure. We indicated that the combination with hemodialysis may enhance the efficacy and safety of the treatment for several reasons. (i) Enhanced oxalate clearance: in patients with PH, dialysis can help remove the excess oxalate that has already been produced, while lumasiran reduces the production of new oxalate. This combination therapy provides a dual mechanism, both reducing production and increasing elimination. (ii) Improved renal function: in the included single-arm studies, in patients who already had renal damage or were nearing renal failure (Michael *et al*. patients eGFR baseline: 16.5 mL/min/1.73 m^2), merely reducing oxalate production may not be sufficient to rapidly alleviate the burden on the kidneys. Regular hemodialysis to remove accumulated toxins can help improve or stabilize renal function, thereby enhancing the overall effectiveness of the treatment. (iii) Enhanced patient safety and tolerability: hemodialysis can control and optimize the body's electrolyte and acid–base balance, which is particularly important for the management of oxalates. By optimizing these parameters, potential side effects associated with lumasiran treatment can be reduced, enhancing overall treatment safety.

To make the study more comprehensive, we fully discussed the involved case report of RNAi therapy in PH. Although it included a relatively small number of patients, those studies provide several valuable insights into the treatment strategies for PH. Patients with PH who underwent kidney transplantation combined with RNAi therapy, using agents such as lumasiran or nedosiran, demonstrated significant therapeutic benefits. This combination approach shows a curative effect by reducing systemic oxalate burden and improving transplant outcomes, suggesting that RNAi therapy enhances the success of transplantation by mitigating the risks associated with oxalate overproduction. The mechanism of action of RNAi therapy warrants particular attention. Lumasiran and nedosiran, as RNAi drugs targeting the oxalate metabolic pathway, significantly reduce PO and urinary oxalate levels by inhibiting the expression of the oxalate synthase gene, thereby reducing oxalate deposition in the kidneys [49]. This effect is especially crucial for post-transplant patients, as reducing the oxalate burden effectively protects the graft and reduces the risk of graft injury [50]. Therefore, the application of kidney transplantation combined with RNAi therapy in PH patients has shown substantial clinical potential. Early clinical intervention in neonates diagnosed antenatally with PH1 represents a significant therapeutic innovation. The early use of RNAi therapy, such as lumasiran, in newborns has demonstrated considerable clinical benefits, including complete remission of both PO and urinary oxalate levels and rapid recovery of renal function. These findings underscore the importance of early diagnosis and timely therapeutic intervention, which can effectively halt disease progression and improve the long-term prognosis for PH1 patients [51]. Early intervention in neonates helps prevent oxalate accumulation at an early stage, thereby reducing irreversible kidney damage and supporting the effectiveness of this early intervention strategy. The involved study population ranged from birth to 40 years of age, revealing significant age-dependent differences in treatment outcomes with RNAi therapy. In neonates and young children, treatment with lumasiran led to complete remission of PO and urinary oxalate levels, and rapid recovery of renal function. In contrast, adult patients exhibited less pronounced improvements, likely due to more advanced disease progression and prolonged exposure to hyperoxaluria. Early-stage hyperoxaluria in infants is more amenable to favorable outcomes with prompt intervention, as renal function is still relatively intact, facilitating a more effective recovery. These results indicate that age and early disease detection significantly impact treatment outcomes, with early intervention being a key determinant of therapeutic success. The combination of hemodialysis, kidney transplantation and pharmacological treatment (such as RNAi therapy) has been effective in reducing PO and urinary oxalate levels. This multimodal approach not only reduces oxalate burden but also minimizes the recurrence of nephrolithiasis, thereby improving overall patient outcomes. Hemodialysis helps rapidly reduce PO levels in the acute phase, while RNAi therapy and kidney transplantation ensure long-term management and control of oxalate burden. The success of this multimodal treatment strategy lies in the synergistic effects of the various treatment modalities, which effectively lower systemic oxalate levels and minimize the occurrence of oxalate-related complications. In conclusion, these case report studies support the use of RNAi therapy combined with kidney transplantation and other adjunctive treatments as a comprehensive treatment strategy to improve long-term survival and quality of life in PH patients. Early diagnosis and intervention are particularly important in neonates, significantly improving disease prognosis [52]. Future research should further evaluate the applicability of this multimodal approach across different PH subtypes and in larger patient populations to validate and extend the generalizability of these preliminary findings.

There were several potential limitations in the meta-analysis. Firstly, although we undertook subgroup analysis on treatment duration, dose and drug, some subgroups still had high heterogeneity. Secondly, some of the data were extracted from published images as the original author did not provide detailed appendices. Although this method may introduce some bias, this may also be part of the reason for the large heterogeneity. Thirdly, the number of involved patients was still small and limited, most of the research centered on the lumasiran therapy, and the related clinical trials are still ongoing.

CONCLUSION

This systematic review and meta-analysis study indicated the beneficial effects and safety of RNAi therapy in the treatment

of PH patients in single-arm studies and placebo-controlled trial studies, as well as some case reports. We divided these results into two parts: RNAi therapy–associated AEs and therapy effect. The enrolled studies indicated that early RNAi intervention is beneficial for patients, especially in maintaining stable kidney function and reversing the effects of hyperoxaluria. Furthermore, the high-dose and long time-duration RNAi therapy may have a better clinical effect. The efficacy and safety of RNAi combined with hemodialysis seems to be promising, and it deserves more well-designed trials with large sample sizes in the future. RNAi therapy plays an important role in the treatment of PH.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

ACKNOWLEDGEMENTS

We are very grateful to Professor Yaacov Frishberg, Sally and Wesley Hayes *et al*. for designing and conducting the clinical trials reviewed here, which have provided us with invaluable frontline data.

FUNDING

The Tianjin Health Science and Technology Project (TJWJ2022MS005), and the Kidney Medical development research Fund (SO.20220718 TJ).

DATA AVAILABILITY STATEMENT

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

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Received: 9.7.2024; Editorial decision: 14.11.2024