Annals of Pharmacy Practice and Pharmacotherapy
ISSN: 3062-4436
2025, Volume 5, Issue 2, Page No: 147-153

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Hydroxychloroquine and Hematuria Improvement in Children with X-Linked Alport Syndrome: A Retrospective Case Series

Hiroshi Nakamura[1]*, Yuta Kato[1]

[1]Department of Pharmacotherapy and Pharmacy Services, Faculty of Pharmacy, Nagoya University, Nagoya, Japan.

***E-mail** ✉ hiroshi.nakamura@outlook.com

Received: 21 August 2025; **Revised:** 25 November 2025; **Accepted:** 28 November 2025

ABSTRACT

X-linked Alport syndrome (XLAS) is a rare hereditary nephropathy characterized by defects in type IV collagen. It represents the most common subtype of Alport syndrome, with an estimated prevalence of around 1 in 10,000, roughly fourfold higher than autosomal recessive forms. Here, we describe eight pediatric patients with XLAS who exhibited ongoing hematuria and proteinuria and report their outcomes after hydroxychloroquine (HCQ) administration to assess its potential as an early treatment strategy. This retrospective study evaluated 8 patients diagnosed with XLAS who presented with persistent hematuria and proteinuria at varying ages of disease onset and received hydroxychloroquine (HCQ) therapy. Urinary erythrocyte counts and urinary albumin levels were assessed. Descriptive analyses were applied to characterize treatment response to HCQ at 1, 3, and 6 months of follow-up. Following 1, 3, and 6 months of hydroxychloroquine (HCQ) therapy, reductions in urinary erythrocyte counts were observed in 4, 7, and 8 children, respectively. A decline in proteinuria was noted in 2, 4, and 5 patients at the corresponding time points. One patient developed increased proteinuria after 1 month of treatment; this elevation persisted at 3 months but subsequently decreased to a minimal level by the 6-month follow-up. We report the first evidence suggesting a potential therapeutic effect of hydroxychloroquine (HCQ) in XLAS patients with hematuria and persistent proteinuria. The findings indicate that HCQ may help reduce both hematuria and proteinuria.

Keywords: Therapy, Hydroxychloroquine, Proteinuria, X-linked Alport syndrome, Hematuria

How to Cite This Article: Nakamura H, Kato Y. Hydroxychloroquine and Hematuria Improvement in Children with X-Linked Alport Syndrome: A Retrospective Case Series. Ann Pharm Pract Pharmacother. 2025;5(2):147-53. https://doi.org/10.51847/ZsED0JMPnV

Introduction

A clinical triad consisting of hematuria, hearing impairment, and ocular abnormalities was first described by Arthur C. Alport in 1927 and later defined as Alport syndrome [1]. This rare inherited disorder has an estimated incidence ranging from 1 in 5,000 to 1 in 50,000 individuals [2]. Among its three genetic subtypes—X-linked, autosomal recessive, and autosomal dominant—X-linked Alport syndrome (XLAS) is the most prevalent, accounting for approximately 80%–85% of cases. XLAS results from mutations in the COL4A5 gene, which encodes the α5 chain of type IV collagen [3]. These genetic alterations lead to reduced expression of the α5 chain within the glomerular basement membrane [4]. The prevalence of XLAS is estimated at approximately 1 in 10,000 individuals, which is higher than that of the autosomal recessive and autosomal dominant forms [2].

Pathogenic variants in COL4A5 impair glomerular filtration barrier function. Clinically, XLAS typically begins with isolated microscopic hematuria, then progresses to albuminuria, and finally to overt proteinuria. Over time, affected individuals may ultimately develop end-stage renal disease. In males with XLAS, the risk of kidney failure is estimated to reach approximately 50% by age 25, 90% by age 40 years, and nearly 100% by age 60 [5]. To date, management of XLAS and delay of progression to kidney failure remain challenging. Although interventions such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (AT1

antagonists), and other renin–angiotensin–aldosterone system (RAAS) inhibitors can delay the onset of proteinuria and renal decline, no curative therapy currently exists for Alport syndrome [6-9]. Moreover, gene therapy approaches remain uncertain regarding their clinical feasibility [10]. Therefore, identifying novel therapeutic strategies for this important cause of pediatric kidney failure remains a priority.

Hydroxychloroquine (HCQ), an established immunomodulatory agent used in systemic lupus erythematosus and rheumatoid arthritis [3], may be relevant to the treatment of XLAS. Its use in this context was initially prompted by the clinical course of a 17-year-old female patient (Patient No. 1) with a seven-year history of persistent macroscopic hematuria and proteinuria. Renal biopsy in this patient revealed glomerular IgA deposition (++), and she was subsequently treated with HCQ. Unexpectedly, a marked clinical improvement was observed following therapy: macroscopic hematuria resolved after one month and remained stable after six months of treatment. In parallel, proteinuria, assessed by urinary albumin excretion index, decreased from + to negative within three months of HCQ therapy.

More recently, HCQ has been investigated in immunoglobulin A nephropathy (IgAN) [11]. A randomized controlled trial demonstrated that HCQ added to optimized RAAS inhibition significantly reduced proteinuria in IgAN patients over six months without reported adverse effects [12]. Similar to IgAN, inflammatory processes and fibrosis are believed to contribute significantly to disease progression in Alport syndrome. HCQ may therefore exert beneficial effects through its anti-inflammatory and immunomodulatory properties.

In this context, the present study describes a cohort of eight children with XLAS who presented with persistent hematuria and proteinuria at varying ages of onset and were subsequently treated with HCQ at different stages of disease. The clinical outcomes following therapy were analyzed to explore the potential efficacy of HCQ as an early intervention in XLAS.

Materials and Methods

This retrospective analysis included eight pediatric patients with XLAS who exhibited persistent hematuria and proteinuria at different ages of onset and subsequently received hydroxychloroquine (HCQ). The inclusion criteria were: (i) age 0–18 years with a confirmed diagnosis of XLAS, and (ii) persistent hematuria with proteinuria and treatment with HCQ. Patients receiving HCQ for less than six months were excluded.

After approval from the Ethics Committee of Shanghai Children's Hospital (No. 2019R063-E02) and obtaining written informed consent from parents or guardians, all eight children (five boys and three girls) were enrolled and treated with HCQ between January 2019 and June 2021. At baseline, all patients had already been followed for more than six months and were receiving either benazepril or valsartan therapy.

Retrospective data collection included sex, age at symptom onset, age at HCQ initiation, age at onset of microalbuminuria, age at progression to overt proteinuria, family history, and the presence of hearing or ocular abnormalities. Available renal pathology data were also reviewed. In cases of unexplained persistent glomerular hematuria, renal biopsy was recommended. Given the established relationship between COL4A5 mutations and disease severity, as well as the correlation between genotype and age at kidney failure in males with XLAS,9 genetic information was also collected to support diagnosis and enable genotype–phenotype correlation analysis.

The diagnosis of XLAS was established through a joint evaluation by renal pathologists and pediatric nephrologists at Shanghai Children's Hospital. Suspicion was raised in patients with persistent glomerular hematuria, particularly when accompanied by a family history of Alport syndrome or renal failure, or when characteristic extrarenal features such as hearing loss, lenticonus, or retinal abnormalities were present. Confirmation was based on the absence of the collagen IV α5 chain in the glomerular basement membrane, lack of this chain in skin tissue, or identification of a pathogenic COL4A5 variant.

Next-generation sequencing of all exons and exon–intron boundaries was performed in six patients, identifying five missense mutations and one deletion in COL4A5 **(Table 1).** All patients had preserved renal function at baseline, were previously healthy, and had not received HCQ before inclusion.

Table 1. Characteristics of the eight patients.

Patient ID	Sex	Age at renal biopsy (yr)	Age at enrollment (yr)	Age at onset (yr)	Genetic variant*	Collagen IV findings	Immunofluorescence results	Electron microscopy findings	Prior therapy
1	Female	11.5	17	9.7	COL4A5 c.688G > A	Absence of α5(IV) chains in kidney	IgA (++)	Mild glomerular alterations	Benazepril
2	Male	ND	10.5	3.6	ND	Absence of α5(IV) chains in skin	ND	ND	Benazepril
3	Male	2.8	3.3	2.1	COL4A5 c.2404G > A	Absence of α5(IV) chains in kidney	(−)	Mild glomerular alterations	Valsartan
4	Male	5.3	9.8	2	COL4A5 c.4688G > A	Absence of α5(IV) chains in kidney	(−)	Mild glomerular alterations	Valsartan
5	Female	12.6	16.5	2	COL4A5 EX3_36DEL	Absence of α5(IV) chains in kidney	IgA (±)	Irregular thickness of the glomerular basement membrane	Valsartan
6	Male	3.7	5.2	0.9	ND	Absence of α5(IV) chains in skin	(−)	Slight mesangial proliferation	Benazepril
7	Male	6.2	9.8	2	COL4A5 c.2641G > A	Absence of α5(IV) chains in kidney	(−)	Slight mesangial proliferation	Valsartan
8	Female	9.5	12	3.8	COL4A5 c.1259G >A	Absence of α5(IV) chains in kidney	(−)	Irregular thickness of the glomerular basement membrane	Valsartan

Note: *Reference genome GRCh37 (hg19). Abbreviation: ND = not performed.

All XLAS patients received oral hydroxychloroquine at a dose of 6.5 mg/kg twice daily for a minimum duration of six months. Before HCQ initiation, patients No. 1, 2, and 6 had been treated with benazepril, while the remaining patients had received valsartan. During HCQ therapy, all patients continued benazepril at a stable dose of 2–4 mg/m²/day, which was not modified throughout the six-month treatment period. Changes in hematuria were monitored using urinary erythrocyte counts obtained from first-morning urine samples after treatment initiation. Proteinuria was assessed through urinary albumin characterization in first-morning urine. Patients were advised to attend outpatient follow-up for monthly first-morning urine testing. Urine samples were not collected during episodes of infection.

Hematuria severity was classified into three levels based on urinary erythrocyte counts: >100/high-power field (HPF), 50–100/HPF, and < 50/HPF. Proteinuria was categorized into six grades according to urinary albumin levels: − (negative, <10 mg/dL), ± (trace, 10–20 mg/dL), +P (30 mg/dL), ++P (100 mg/dL), +++P (300 mg/dL), and ++++P (1000 mg/dL).

Treatment outcomes at 1, 3, and 6 months of HCQ therapy were retrospectively collected. Liver and renal function tests, as well as ophthalmological examinations, were also reviewed to monitor potential adverse effects of HCQ. Descriptive statistics were applied to describe changes in hematuria and proteinuria over time following treatment initiation. Differences in the severity of hematuria and proteinuria among the eight patients were assessed using the Chi-square test.

Results and Discussion

Study participants

The clinical features and family pedigree information of the eight included cases are presented in **Table 1**. Age at disease onset ranged from 0.9 to 9.7 years, while age at study inclusion ranged from 3.3 to 17 years. All patients exhibited renal involvement characterized by varying degrees of hematuria and proteinuria.

Patients No. 1 and No. 3 presented with gross hematuria accompanied by only mild glomerular changes, whereas the remaining six patients had microscopic hematuria. Except for Patient No. 2, all other cases demonstrated glomerular abnormalities and/or mesangial proliferation.

Patient outcome

After 1 month of HCQ therapy, gross hematuria resolved in both patients who initially presented with macroscopic bleeding (Patient No. 1 and No. 3). In addition, urinary erythrocyte counts decreased in four patients (No. 1–4), with this improvement maintained throughout the 6-month follow-up period **(Table 2).**

For the remaining four patients (No. 5–8), a general reduction in urinary erythrocyte counts was observed at the 3-month evaluation, with further decreases noted by 6 months **(Table 2).** Overall, the number of patients with reduced urinary erythrocyte counts increased from 4 to 8 during HCQ treatment, as illustrated in **Figure 1** and further supported by **Figure 2.** A statistically significant decline in hematuria severity was observed over the treatment period ($p < 0.05$).

In parallel, the number of patients with decreased proteinuria increased from 2 to 5 over time after HCQ initiation, although one patient initially showed an increase in proteinuria.

Table 2. The responses of the eight patients to HCQ.

Patient No.	Baseline			At 1 month			At 3 months			At 6 months		
	Gravity	Erythrocyte#	Proteinuria*	Gravity	Erythrocyte#	Proteinuria*	Gravity	Erythrocyte#	Proteinuria*	Gravity	Erythrocyte#	Proteinuria*
1	1.018	>100	+ P	1.015	10–15	+ P	1.011	15–25	–	1.020	15–25	–
2	1.021	>100	++++ P	1.022	75–100	+++ P	1.022	15–25	+++ P	1.022	25–35	+++ P
3	1.024	>100	+ P	1.020	10–15	+ P	1.018	10–15	+ P	1.025	10–15	+ P
4	1.015	75–100	++P	1.010	5–10	+ P	1.016	25–35	+ P	1.018	3–5	++ P
5	1.015	35–50	+ P	1.026	35–50	+ P	1.022	35–50	+ P	1.015	5–10	±
6	1.019	>100	–	1.020	>100	+ P	1.015	75–100	+ P	1.010	15–25	±
7	1.020	>100	+++ P	1.018	>100	+++ P	1.024	25–35	+ P	1.022	35–50	±
8	1.026	50–75	±	1.025	50–75	±	1.028	35–50	±	1.025	25–35	–

Notes: # Urinary erythrocyte count (/HPF), * Urinary albumin classification.

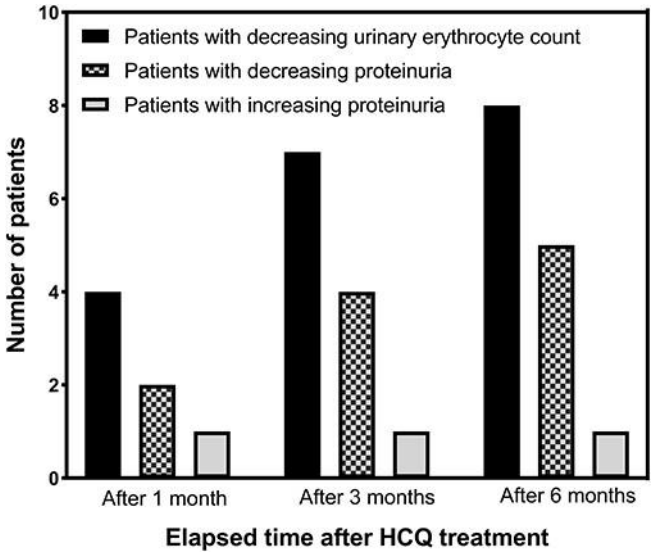

Figure 1. Changes in the number of patients over time following HCQ treatment.

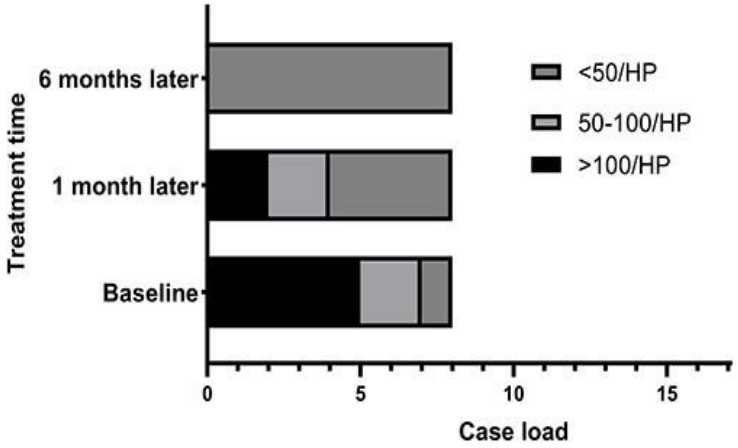

Figure 2. Hematuria outcomes in the eight patients receiving HCQ therapy ($P < 0.05$). Hematuria severity was classified into three grades based on urinary erythrocyte counts (> 100/HPF, 50–100/HPF, and <50/HPF). After 6 months of treatment, all patients remained at < 50/HPF.

All patients showed normal liver and renal biochemical parameters throughout the 24-week HCQ treatment period. No significant changes in eGFR were observed. Ophthalmologic examinations and visual assessments remained normal after therapy. No severe adverse events were reported during treatment.

In this cohort of eight children with XLAS exhibiting varying degrees of hematuria and proteinuria, HCQ therapy was associated with a marked reduction in hematuria across all patients. Proteinuria decreased in five patients after 6 months of treatment, while the remaining three showed stable protein levels. It should be noted that limitations in the precision of urinary protein assessment may have influenced the proteinuria-related analyses, and the small sample size may also have affected statistical power.

At present, no curative treatment for XLAS is available [13, 14]. Current RAAS inhibition therapy can only delay the progression of clinical manifestations [9]. Recently, several novel agents have been investigated for Alport syndrome (AS), including bardoxolone methyl and lademirsen, which have attracted considerable attention [13]. Bardoxolone methyl, an Nrf2 pathway activator with antioxidant and anti-inflammatory properties, was evaluated in the CARDINAL trial (NCT03019185) [15]. A completed phase II study demonstrated that bardoxolone methyl increased estimated glomerular filtration rate (eGFR) in patients with AS [16]. This agent may therefore be particularly relevant for patients with declining renal function. However, bardoxolone methyl has also been shown to increase albuminuria, which is associated with a higher risk of progression to kidney failure [16]. Consequently, its use may be less suitable in younger patients with preserved GFR [17].

Lademirsen (SAR339375), investigated in the HERA trial (NCT02855268), targets microRNA-21 expression in the kidney. MicroRNA-21 regulates inflammatory and fibrotic pathways. Given that the decline in GFR in AS is

closely linked to interstitial fibrosis and tubular atrophy, anti-fibrotic and anti-inflammatory strategies such as lademirsen may offer potential benefit, particularly in younger patients [18, 19].

Similarly, hydroxychloroquine possesses anti-inflammatory and immunomodulatory properties. It has been shown to reduce the production of pro-inflammatory cytokines, including TNF-α, IL-6, and IFN-α [20, 21]. Suppression of these mediators may attenuate mesangial cell–mediated inflammatory responses, which are thought to contribute to downstream podocyte and tubular injury. Through this mechanism, HCQ may help mitigate renal damage, although its exact role in the inflammatory pathways of XLAS remains unclear. Further studies with larger cohorts are required to clarify this relationship.

Hydroxychloroquine is also associated with a broad spectrum of adverse effects, including cardiovascular, dermatological, gastrointestinal, hematological, metabolic, and ophthalmological toxicities [22]. Both the dose and the duration of therapy influence these adverse events. Determining an optimal balance between efficacy and safety is therefore essential. In our study, low-dose, short-term HCQ administration appeared to be safe in the pediatric population.

Conclusion

In this case series, we evaluated the efficacy and safety of hydroxychloroquine (HCQ) in combination with RAAS inhibition in eight patients with XLAS presenting with hematuria and persistent proteinuria. Overall, HCQ appears to represent a potential therapeutic approach for reducing hematuria and proteinuria in XLAS. The patients demonstrated good tolerance and adherence to the combined HCQ and RAAS inhibitor regimen.

However, the study is limited by its retrospective design and the small number of included patients. Larger, high-quality evidence-based studies are required to confirm these findings. To further investigate the role of HCQ in pediatric XLAS, a randomized controlled trial has been registered at ClinicalTrials.gov (NCT04937907).

Acknowledgments: Every stage of this research received funding from the Shanghai Municipal Commission of Science and Technology (grant number 19ZR1442300) and Shanghai Children's Hospital (grants 2021YQ04 and 2021YGZQ06). The authors also express their appreciation to the patients and their families for their support.

Conflict of Interest: None

Financial Support: None

Ethics Statement: The study was carried out in accordance with the ethical principles of the Declaration of Helsinki.

The participants provided consent for the submission of this study for publication in the journal.

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