it is believed to be approximately 1 to 9 per 100,000 people (1). Alport syndrome is phenotypically heterogeneous and results from various patterns of genetic inheritance of mutations in type IV collagen genes (COL4A3, COL4A4, and COL4A5). The most common form is an X-linked mutation in COL4A5, which accounts for 80% of Alport syndrome. Inheritance may also be autosomal recessive and autosomal dominant. More rarely, Alport syndrome can be inherited as an X-linked or autosomal-dominant disease (2). In recent guidelines developed by Kashtan and Gross (3), genetic testing is recommended in suspected Alport syndrome patients at the time of diagnosis, unless diagnosis is before the ages of 12–24 months. Female X-linked and all autosomal-dominant patients are less likely to develop CKD; therefore, it is suggested that ACE inhibitor/ARB treatment begin at the onset of microalbuminuria (3).

Although variable, the natural course of Alport syndrome progresses from hematuria to albuminuria, followed by proteinuria, glomerular and tubulointerstitial fibrosis, decline in estimated glomerular filtration rate (eGFR), and kidney failure. Current treatment recommendations for Alport syndrome focus on slowing this progression of kidney disease (Table 1).

The current standard of care for patients with Alport syndrome includes the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). The recent Efficacy and Safety Study to Delay Renal Failure in Children with Alport Syndrome (Early PROTECT) trial demonstrated that early treatment with the ACE inhibitor ramipril reduced the albuminuria slope and delayed the decline in eGFR in children with Alport syndrome (2). In recent guidelines developed by Kashtan and Gross (3), genetic testing is recommended in suspected Alport syndrome patients with clinical or pedigree data suggesting a diagnosis of Alport syndrome to help guide treatment. In male X-linked and all patients with autosomal-recessive Alport syndrome, progression to CKD is more likely, and it is suggested that ACE inhibitor/ARB treatment begin at the time of diagnosis, unless diagnosis is before the ages of 12–24 months. Female X-linked and all autosomal-dominant patients are less likely to develop CKD; therefore, it is suggested that treatment with ACE inhibitors/ARBs should begin at the onset of microalbuminuria (3).

Several novel therapeutic agents for the treatment of Alport syndrome are currently being investigated. The Phase 2/3 Trial of the Efficacy and Safety of Bardoxolone Methyl in Patients with Alport Syndrome (CARDINAL) is a recently completed clinical trial that compared the efficacy and safety of bardoxolone methyl to placebo in patients with Alport syndrome and CKD. Bardoxolone methyl is an oral agent that activates transcription factor Nrf2 and inhibits

### Treatment Updates in Alport Syndrome

By Mairead Pfaff and Christine B. Sethna

Alport syndrome is an inherited kidney disease characterized by abnormalities in the glomerular basement membrane and is associated with hearing loss, ocular anomalies, and risk for progressive loss of kidney function. Alport syndrome accounts for 3% of children with chronic kidney disease (CKD) and 0.2% of adults with kidney failure in the United States (1). The exact prevalence of Alport syndrome is unknown, but

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Sam Kant reports no disclosures. Dwurau Geetha has the following disclosures: site principal investigator for the ADVOCATE trial and consultant to Chemocentryx (manufacturer of Avacopan) and Austria Pharmaceuticals Inc.

### References

Alport Syndrome

Continued from page 25

its nuclear factor-κB, thereby inducing anti-inflammatory molecular pathways, restoring mitochondrial function, and reducing oxidative stress. In a recent press release, Reata Pharmaceuticals announced positive results for the primary outcome, achieving a statistically significant improvement in eGFR of 7.7 mL/min/1.73 m² from baseline after 2 years in Alport syndrome patients with CKD treated with bardoxolone methyl compared to placebo (4). Additionally, Reata reported the results of the long-term extension trial, Extended Access Program for Bardoxolone Methyl in Patients with CKD (EAGLE), which also showed favorable outcomes with improvement in eGFR in 14 patients after 3 years of treatment (4). Bardoxolone was reported to be well tolerated, with muscle spasms and elevated aminotransferases observed as the most common adverse events. These data have not yet been peer reviewed or published. The company announced that it will be seeking US Food and Drug Administration (FDA) approval.

Additionally, the use of microRNA (miRNA)-based treatments has been of interest after clinical evidence of increased levels of miRNA-21 was determined to contribute to kidney fibrosis in Alport syndrome (5, 6). A phase 2 randomized, double-blind, placebo-controlled study of lademirsen, an anti-miRNA-21 given by subcutaneous injection, is currently underway. The study, sponsored by Sanofi, has a target enrollment of 45 patients, and results are expected to be available in 2023 (7).

Atrasentan in Patients with Proteinuric Glomerular Diseases (AFFINITY) is a phase 2 open-label basket trial of atrasentan, an oral selective endothelin A receptor blocker agent. AFFINITY is set to begin recruitment in the first half of 2021. Chinook Therapeutics plans to recruit 80 participants with Alport syndrome, along with another proteinuric kidney diseases (8).

Overall, there have been many new developments in the diagnosis and treatment of Alport syndrome and promising clinical trials are underway. With these potential treatment options becoming available in the future, it is even more important that early diagnosis of Alport syndrome aided by genetic testing becomes more widely available and affordable. More research must be done to corroborate the guidelines regarding treatment paths for specific Alport syndrome genotypes. Last, with the recent increase in research for Alport syndrome, ongoing and upcoming trials should consider opinions of key stakeholders, including clinicians and patients, when planning clinical trials (9).

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The authors report no conflicts of interest for any of the medications discussed in the article.

References


4. Reata Pharmaceuticals. Reata Announces Positive Results from Year 2 of the Pivotal Phase 3 CARDINAL

Table 1. Drugs to treat Alport syndrome

Summary of drugs currently used to treat Alport syndrome

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Indication for treatment</th>
<th>Method of delivery</th>
<th>Mechanism of action</th>
<th>Possible side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin Converting Enzyme (ACE) Inhibitors</td>
<td>XLAS males—at time of diagnosis; XLAS females—microalbuminuria; ARAS—at time of diagnosis; ADAS—albuminuria</td>
<td>Oral</td>
<td>Inhibits ACE and prevents formation of angiotensin II; allows relaxation of blood vessels, decreases blood pressure, and decreases sodium levels in the blood</td>
<td>Dizziness, dry cough, angioedema, hyperkalemia, elevated creatinine</td>
</tr>
<tr>
<td>Angiotensin Receptor Blockers</td>
<td>Patients with persistent proteinuria after taking ACE inhibitors or patients who did not tolerate ACE inhibitors due to side effects</td>
<td>Oral</td>
<td>Blocks aldosterone from binding receptor, increasing excretion of water and sodium, retaining more potassium, decreasing blood pressure</td>
<td>Dizziness, angioedema, hyperkalemia, elevated creatinine</td>
</tr>
</tbody>
</table>

Bardoxolone Methyl (RTA 402)

Cardinal trial: phase 3 trial of 157 Alport syndrome (AS) patients randomized to bardoxolone or placebo for 100 weeks was completed in October 2020.

Eagle trial: long-term extension trial of 14 AS patients treated with bardoxolone for 3 years.

Lademirsen (RG-012, SAR339375)

Genzyme, a Sanofi Company

A phase 2, randomized, double-blind, placebo-controlled study has a target enrollment of 45 participants. Study is actively recruiting.

Atrasentan (CHK-01, Atrasentan Hydrochloride, ABT-627)

Chinook Therapeutics

Afinity study: phase 2, open-label basket study to evaluate the efficacy and safety of atrasentan; set to begin recruitment in the first half 2021.

Table 2. Drugs currently being studied to treat Alport syndrome

Summary of drugs currently being studied to treat Alport syndrome

<table>
<thead>
<tr>
<th>Drug/Company</th>
<th>Stage of development</th>
<th>Method of delivery</th>
<th>Mechanism of action</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bardoxolone Methyl (RTA 402)</td>
<td>CARDINAL trial: phase 3 trial of 157 Alport syndrome (AS) patients randomized to bardoxolone or placebo for 100 weeks was completed in October 2020.</td>
<td>Oral bardoxolone methyl capsules 5–30 mg QD</td>
<td>Activates the pathway of transcription factor Nrf2 and inhibits nuclear factor-κB pathway. Together, these effects decrease kidney inflammatory responses and prevent fibrosis.</td>
<td>Compared to baseline, eGFR increased 7.7 mL/min/1.73 m² (p = 0.0005) at 100 weeks. eGFR increased 11.5, 13.3, and 11 mL/min/1.73 m² at years 1, 2, and 3, respectively.</td>
</tr>
<tr>
<td>Reata Pharmaceuticals</td>
<td>EAGLE trial: long-term extension trial of 14 AS patients treated with bardoxolone for 3 years.</td>
<td>Weekly subcutaneous injection of the anti-miRNA-21 drug</td>
<td>MicroRNA-21 reduces P42/P44 MAPK pathway activation and therefore reduces renal fibrosis and inflammation.</td>
<td>Adverse events</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>Annualized change in eGFR from baseline to 48 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Change in urinary protein-to-creatinine ratio from baseline to week 12</td>
</tr>
</tbody>
</table>
D rugs cause approximately 20% of community- and hospital-acquired episodes of acute kidney failure (1–3). Among older adults, the incidence of drug-induced nephrotoxicity may be as high as 66% (4). Drug-induced nephrotoxicity is to be approximately 14%–26% in intensive care unit cohorts (5–7).

A growing body of literature highlights the potential for drugs to induce not only AKI but also glomerular diseases, termed drug-induced glomerular diseases. Patients with glomerular involvement generally present with one of five clinical syndromes: acute current macroscopic hematuria, microscopic hematuria associated with proteinuria, heavy proteinuria or nephritic/nephropathy syndrome, rapidly progressive glomerulonephritis (RPGN), or chronic glomerulonephritis (CGN). Strict monitoring of kidney function, urine and blood abnormalities, and blood pressure must be performed in patients undergoing therapy with potentially toxic drugs. It is critical to recognize these conditions early, because in many patients, there is improvement after removing the offending medication (8). In certain scenarios, removal of the offending agent plus an immunosuppressive strategy has been employed. However, the effectiveness of immunosuppressive therapy in this context has not been determined. From a diagnostic and therapeutic standpoint, it is sometimes difficult to attribute a drug as being directly causative versus unmasking a preexisting syndrome. Drug-induced glomerular diseases can also be classified into two categories: direct cellular toxicity and immune-mediated injury (Table 1).

**Direct glomerular cell injury involving the visceral epithelial (or podocytes), endothelial, and mesangial cells**

**Podocyte injury:** Drug-induced podocytopathies can manifest as nephrotic syndrome, nephrotic-range proteinuria, with or without AKI. The spectrum of pathologic findings has consisted of minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS). This includes both FSGS, not otherwise specified, and collapsing glomerulopathy. Multiple therapeutic agents have been associated with these lesions (Table 1), including interferon, bisphosphonates, lithium, nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., indomethacin, celecoxib), and androgenic anabolic steroids (8).

**Endothelial cell injury:** Thrombotic microangiopathy (TMA) is characterized by mechanical microangiopathic hemolytic anemia, thrombocytopenia, and end organ injury. Pathologic findings include endothelial swelling and necrosis, glomerular and vascular thrombosis, mesangial dysgenesis, glomerular basement membrane duplication with cellular interposition, micosedimal edema, and fibrin deposition (8). Drugs are an important acquired cause of TMA (Table 1) and include anti-angio genesis drugs, chemotherapy, interferons, quinine, calcium channel inhibitors, and thienopyridines (9). It is the interest that drug-induced TMA may be immune mediated (ADAMTS-13 or anti-platelet antibodies induction), a consequence of direct toxicity of the offending drug to endothelial cells and more recently, induction of the vascular endothelial growth factor pathway to involve injury to kidney podocytes (10). Although the majority of patients lack complement genetic variants, the response of drug-induced TMA to eculizumab may provide indirect evidence of complement activation in some cases (11).

**Mesangial cell injury:** Smoking-associated nodular glomerulosclerosis is a lesion related to heavy cigarette smoking (12), and smoking cessation seems to reduce the likelihood of progression to end stage kidney disease (13). Although usually idiopathic, the immunoglobulin A (IgA) antibody is occasionally induced by drugs (e.g., vancomycin, carbamazepine, ceftriaxone, and cyclosporine), malignancies, infections, and other causes (14).

**Immune-mediated injury from drug-induced autoimmunity**

Drug-induced autoimmunity is an idiosyncratic (type B) reaction, which is generally unpredictable and unrelated to the mechanism of action of the drug, unlike the type A reaction, which is drug dependent and dose related (15). Drug-induced autoimmunity is a rare phenomenon, occurring in <1% of patients exposed to a drug, leading to manifestations of lupus or vasculitis; and kidney involvement—even rare—occurs in about 5% of patients with drug-induced autoimmunity (15). Most of the disorders improve upon stopping the medication. In patients where major organ involvement is present, immunosuppression may be needed to reduce the inflammation and prevent permanent damage (16). The mechanism of glomerular injury is thought to be from the activation of the adaptive immune system by the offending drug or its metabolite. There is a lack of evidence of preclinical evidence of drug-induced autoimmunity (16). It is of interest that drug-induced autoimmunity is a rare phenomenon, occurring in <1% of patients exposed to a drug, leading to manifestations of lupus or vasculitis; and kidney involvement—even rare—occurs in about 5% of patients with drug-induced autoimmunity (15). Most of the disorders improve upon stopping the medication. In patients where major organ involvement is present, immunosuppression may be needed to reduce the inflammation and prevent permanent damage (16). The mechanism of glomerular injury is thought to be from the activation of the adaptive immune system by the offending drug or its metabolite. There is a lack of evidence of preclinical evidence of drug-induced autoimmunity (16).

Membranous nephropathy is the other form of drug-induced autoimmunity. Drugs used to treat rheumatoid arthritis, rarely used now including penicillamine and gold salts, were associated with membranous nephropathy. Currently, drug-induced membranous nephropathy is rare and has been reported with organic mercuryals in skin-lightening creams, the newer rheumatoid arthritis drug adalimumab, and NSAIDs including celecoxib (17), gefitinib (18), and nivolumab (19). Interestingly, NSAID-associated membranous nephropathy accounted for 10% of patients with early membranous nephropathy (20). Drug-induced glomerular diseases should be part of the differential diagnosis in patients presenting with glomerular syndrome. Recognition of a drug-induced etiology and rapid withdrawal of the offending agent are essential to optimize the chances of recovery of kidney function. Steroids, immunosuppressants, and/or plasmapheresis may not work in most of these cases. Clinicians must be aware of this clinical presentation in order to individualize patient management.

**References**


