The Rapidly Changing Landscape of IgA Nephropathy Treatment

By Dana V. Rizk

Since the initial description of immunoglobulin A nephropathy (IgAN), significant advances have been made in our understanding of the disease pathogenesis (1). These advances have spurred exciting, new research targeting the various steps in this autoimmune process. But the relatively slow kidney function decline in most IgAN patients has made the implementation of clinical trials with hard outcomes (such as a 50% reduction in estimated glomerular filtration rate [eGFR], kidney failure, or death) quite challenging. In 2016, a partnership between ASN and the US Food and Drug Administration (FDA) identified proteinuria as a surrogate marker of disease progression and response to therapeutic interventions (2). Subsequently, the IgAN community witnessed a renewed interest from the pharmaceutical industry in the treatment of this rare disease and a proliferation of clinical trials (Figure 1). In 2021, the updated Kidney Disease: Improving Global Outcomes (KDIGO) guidelines prioritized clinical trial participation in the hierarchy of disease management strategies (3). Review of all ongoing trials is beyond the scope of this article; it is worth mentioning a few studies that have already yielded exciting results.

The TESTING trial reevaluated the benefit of systemic steroid treatment (4). Use of a lower dose of prednisolone along with antibiotic prophylaxis resulted in favorable kidney outcomes while mitigating serious adverse events. The phase 3 NeftlgAnd trial tested the efficacy of localized steroids at the intestinal mucosal surface where the disease is thought to originate (5). The study showed a 27% relative reduction in proteinuria compared with placebo at 9 months, thought to originate (5). The study showed a 27% relative reduction in proteinuria compared with placebo at 9 months, and RAAS blocker and RAAS blocker.

Another phase 3 trial, PROTECT (6), evaluated the efficacy of sparsentan (a combined angiotensin receptor blocker [irbesartan] and endothelin receptor antagonist) compared with irbesartan alone. The interim results favored sparsentan [irbesartan] and endothelin receptor antagonist) compared

Many other ongoing trials in earlier stages of clinical development are investigating the safety and tolerability of novel therapies targeting B cells (thought to be responsible for the production of the galactose-deficient IgA autoantigen and its autoantibody), as well as the alternative, lectin and terminal complement pathways (9). The rapidly changing treatment landscape in IgAN has energized the nephrology community. Experience gained from current studies will undoubtedly serve as a road map for treating other rare glomerular diseases. Therefore, IgAN patients and their providers have the unique opportunity but also a tremendous responsibility to engage and deliver timely and successful clinical trials.

References

Figure 1. The landscape of clinical trials in IgA nephropathy over the past 3 decades

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Ongoing Trials</th>
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<tr>
<td>Negativa/Toxicity</td>
<td>Fish oil (Donadio)</td>
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<tr>
<td>Pred/Cytoxan/AZA (crescents)</td>
<td>Pred/Cytoxan/AZA (crescents)</td>
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<td>Azathioprine</td>
<td>STOP-IgAN</td>
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<td>Fish oil (Ferraro)</td>
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ACE-inh (Lu), angiotensin-converting enzyme inhibitor (Lu et al.); ACE-inh (Manno), ACE-inh (Manno et al.); AZA, azathioprine; MMF (Houg), mycophenolate mofetil (Houg et al.); MMF (Houg), MMF (Hou et al.); Pred, prednisone; RAAS, renin-angiotensin-aldosterone system; SGLT2, sodium glucose co-transporter 2.