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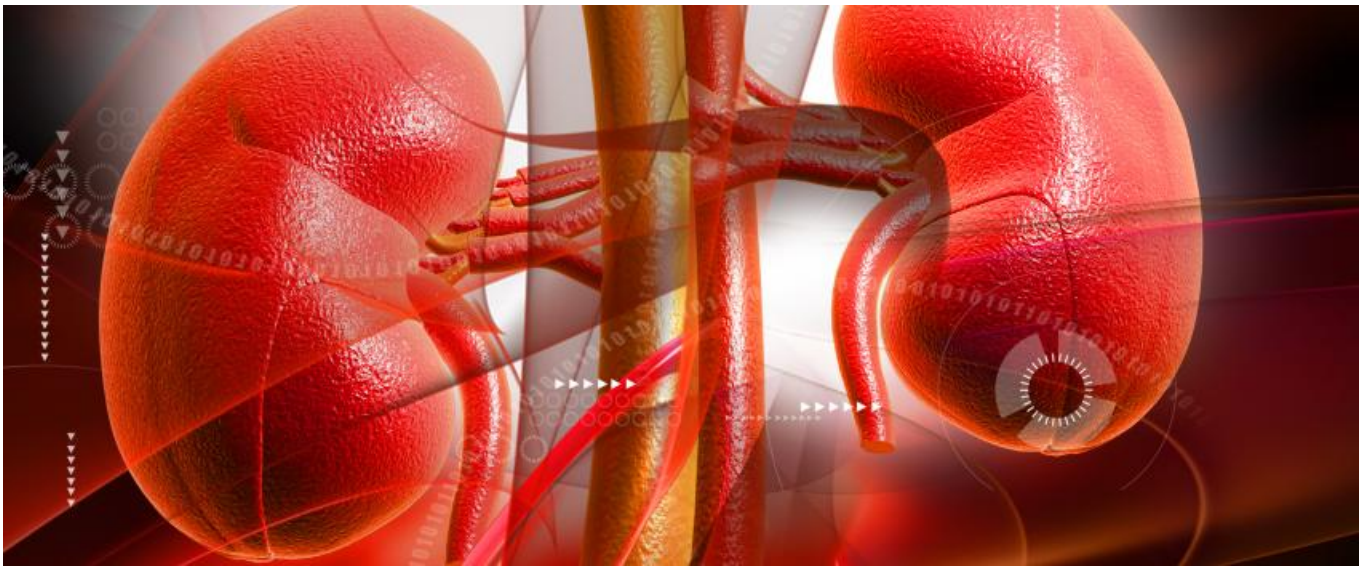
Hope on the horizon for rare kidney disease

Amy Brown



Loosening of clinical requirements has encouraged more projects into the IgA nephropathy pipeline, with a steroid–based approach from Sweden's Calliditas looking particularly promising.

In early 2017, the FDA agreed for the first time that a new surrogate marker could be used to secure approval for a novel approach in IgA nephropathy, a rare form of chronic kidney disease. The decision raised the possibility of considerably shortened developmental timelines and, while not exactly opening the floodgates, the pipeline in this progressive autoimmune condition is now looking fairly healthy.

Two projects are already in pivotal development, Omeros's OMS721 and Nefecon from Calliditas, though data are unlikely to emerge before 2020. Updates from various contenders have come thick and fast in the past few weeks, however, including a potentially fatal stumble by Omeros. It seems there is still much to play for in this underserved orphan indication.

Leading IgA nephropathy projects			
Project	**Company**	**Trial ID (n)**	**Notes**
Phase III			
OMS721	Omeros	NCT03608033 (430)	Data due 2020.
Nefecon	Calliditas	NCT03643965 (450)	Trial to start enrolling imminently; data 2020.
Phase II			
Bardoxolone	Reata	NCT03366337 (100)	Positive phII data reported Sept '18, further development planned.
APL-2	Apellis	NCT03453619 (48)	PhII POC data due H2'18.
Tavalisse	Rigel	NCT02112838 (75)	Update on pivotal programme expected imminently.
LNP023	Novartis	NCT03373461 (48)	Primary completion April '19.
Atacicept	Merck KGaA	NCT02808429 (30)	Primary completion June '21.
Source: EvaluatePharma, company statements, clinicaltrials.gov.			

IgA nephropathy can range in severity and is typically a very slow-moving condition. In some patients it can go unnoticed for years though it is thought that up 40% of those diagnosed will eventually progress to end-stage renal disease (ESRD), something that can take 20 years to occur.

The autoimmune condition occurs when aberrant immunoglobulin A (IgA) antibodies lodge in the kidneys, specifically the glomeruli, causing inflammation and, over time, irreparable damage to the organs. Detection of protein and blood in the urine frequently leads to diagnosis.

Patients at high risk of kidney failure are the target of novel treatments, and are typically described as having stubbornly high levels of proteinuria and deteriorating kidney function. Estimated glomerular filtration rate (eGFR) is considered a pretty reliable indicator of renal damage, but because IgA patients progress so slowly, proving the effectiveness of any intervention has historically presented a very long-term challenge.

Hence the focus on proteinuria, which can be brought down relatively quickly. Work by Calliditas and Tufts University was instrumental in establishing a link between urine protein levels in IgA patients and more dramatic later-stage events like ESRD, and in early 2017 the company was the first to win the FDA's blessing to use change in proteinuria as a primary endpoint in a phase III nephrology trial.

A hit on this surrogate measure will still only lead to accelerated approval, however. For full approval developers must show a benefit on kidney function: eGFR is a surrogate endpoint but is highly predictive of renal failure.

Leading the pack

Calliditas has earned its lead in this space by carrying out the largest successful randomised clinical trial in IgA to date. A 150-patient, phase IIb trial found that Nefecon produced significant reductions in proteinuria and stabilised kidney function, as measured by eGFR. Patients in the placebo group experienced a rise in proteinuria and decline in kidney function.

Nefecon is an oral formulation of the steroid budesonide, delivered in a capsule which has been designed to release the active compound in the ileum. This is the site of the highest concentration of Peyer patches, a lymphoid tissue that is thought to be the source of the problematic IgA antibodies.

"By releasing a very potent autoimmune suppressant right at that very area, the idea is to be disease modifying and hamper antibodies from being produced in the first place," Calliditas's chief executive, Renée Aguiar-Lucander, told *Vantage*.

The systemic steroid prednisone is sometimes used to treat advanced IgA for similar mechanistic reasons, but comes with substantial toxicities. Budesonide has much lower bioavailability, and Calliditas hopes that patients can be treated much earlier in the course of the disease, and with substantially fewer side effects.

The company is now setting out to confirm all this in a global phase III trial, which should treat its first patient very soon.

Coming behind

Omeros, meanwhile, has generated impressive declines in proteinuria with OMS721 in early studies, but the move into phase III on the back of data in only four patients is already looking rash.

The project targets MASP-2, a pro-inflammatory protein involved in activation of the complement system's lectin pathway. Phase II data released last week showed OMS721 having a similar impact on proteinuria as placebo, raising serious questions about this mechanism's relevance in kidney disease.

Looking more promising is Reata's bardoxolone, which last month yielded encouraging data in 23 IgA patients, adding to evidence of efficacy in other forms of kidney disease. The Phoenix study produced an apparent reversal of decline in kidney function over 12 weeks, as measured by eGFR, and the company has pledged to push into later-stage development in the IgA indication.

Bardoxolone is thought to work by activating Nrf2, a transcription factor involved in promoting an antioxidant and anti-inflammatory response. Somewhat uniquely, Reata is focusing on the project's ability to improve kidney function rather than control proteinuria.

"We don't worry about protein endpoints because we directly affect GFR by shutting down inflammation in the glomeruli," the group's chief executive, Warren Huff, told *Vantage*. "We treat the inflammatory pathways and the mitochondrial dysfunction in the kidney."

Still, the fact that bardoxolone does not lower urine protein levels – some studies have detected a rise – has raised concerns. A heart failure signal in a large phase III kidney disease trial several years ago is another red flag, and confirmation of the project's efficacy and safety in larger and longer studies is needed.

Further back

As to what else might be soon be progressing through the clinic, Apellis has said it will report data from the Discovery trial of APL-2 before the end of the year, which includes an IgA cohort. Like Omeros, the company is targeting the complement system, although APL-2 is said to hit all three principal pathways, not just lectin.

Rigel is due to announce shortly whether Tavalisse, a Syk inhibitor, will progress any further in this indication. Disappointing data from a phase II trial were unveiled earlier this year, although the company said a signal was seen in a subgroup of patients with very high proteinuria at baseline.

According to clinicaltrials.gov, data are due next year from a Novartis compound, LNP023, which also targets the complement system, specifically the alternative pathway. Meanwhile Merck KGaA is almost two years into a phase II study of atacicept in IgA; the fusion protein blocks two B cell activating factors thought to be involved in various autoimmune conditions.

The lack of options for IgA points to commercial success for any effective therapy. But this condition spans young and relatively healthy patients, and even in those with more severe disease, progression can be slow. This means it will be paramount for the more novel approaches moving through the clinic to prove that they are safe over the long term, even if the existence of a new surrogate endpoint speeds their path to regulators.