Development of targeted therapies for IgAN: 2024 treatment landscape & beyond

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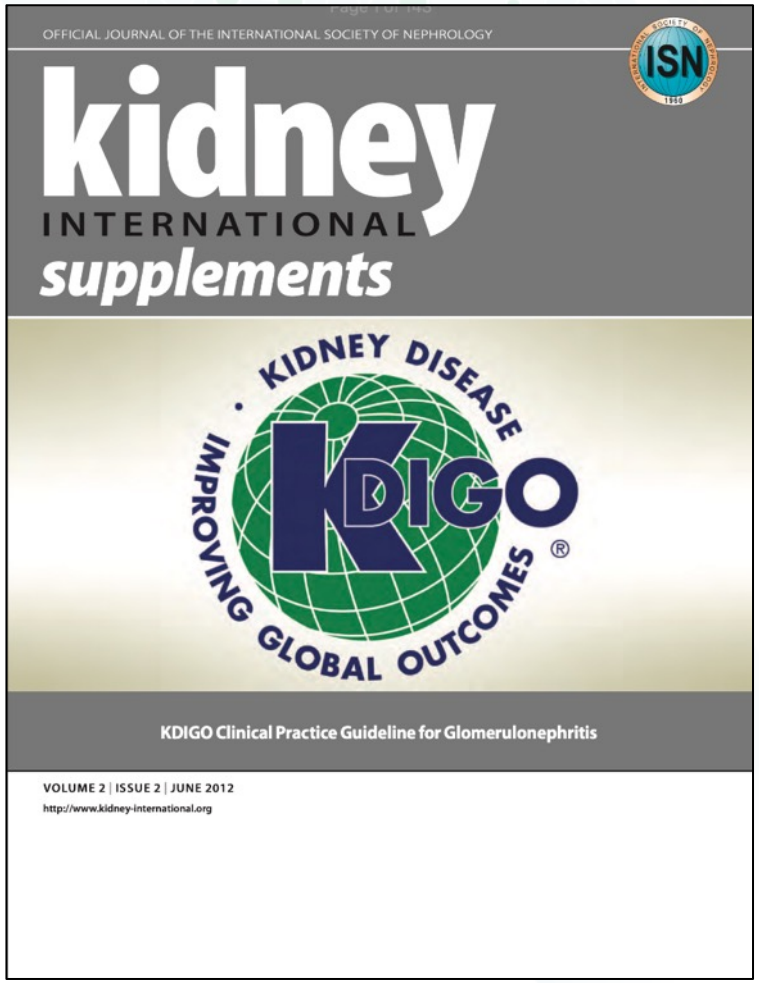
DISCLOSURES

Jonathan Barratt	
Consulting and Speaker Fees	Alexion, Alnylam, Argenx, Astellas, BioCryst, Calliditas, Chinook, Dimerix, Galapagos, Novartis, Omeros, Travere Therapeutics, Vera Therapeutics, Visterra
Grant Support	Alexion, Argenx, Calliditas, Chinook, Galapagos, GlaxoSmithKline, Novartis, Omeros, Travere Therapeutics, Visterra
Clinical trials	ADU-CL-19 & ALIGN (Chinook), APPLAUSE (Novartis), ARTEMIS-IGAN (Omeros), ENVISION (Visterra), NeflgARD (Calliditas), ORIGIN (Vera Therapeutics)
Research projects	Argenx, Calliditas, Chinook, Galapagos, GlaxoSmithKline, Novartis, Omeros, Travere Therapeutics, Visterra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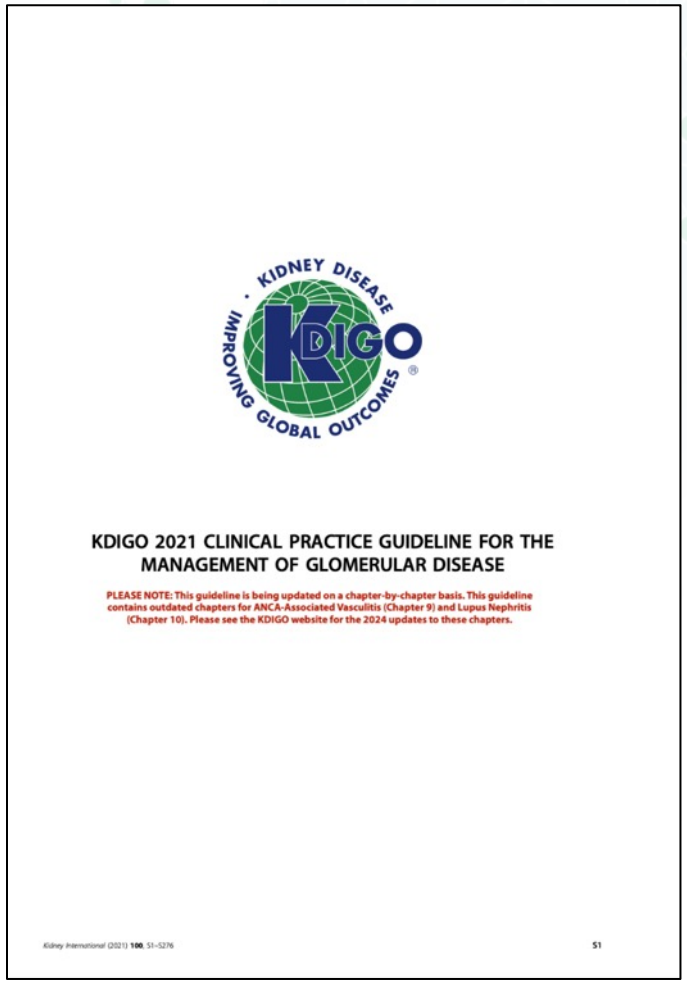
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Kidney International (2021) 100, S1–S276
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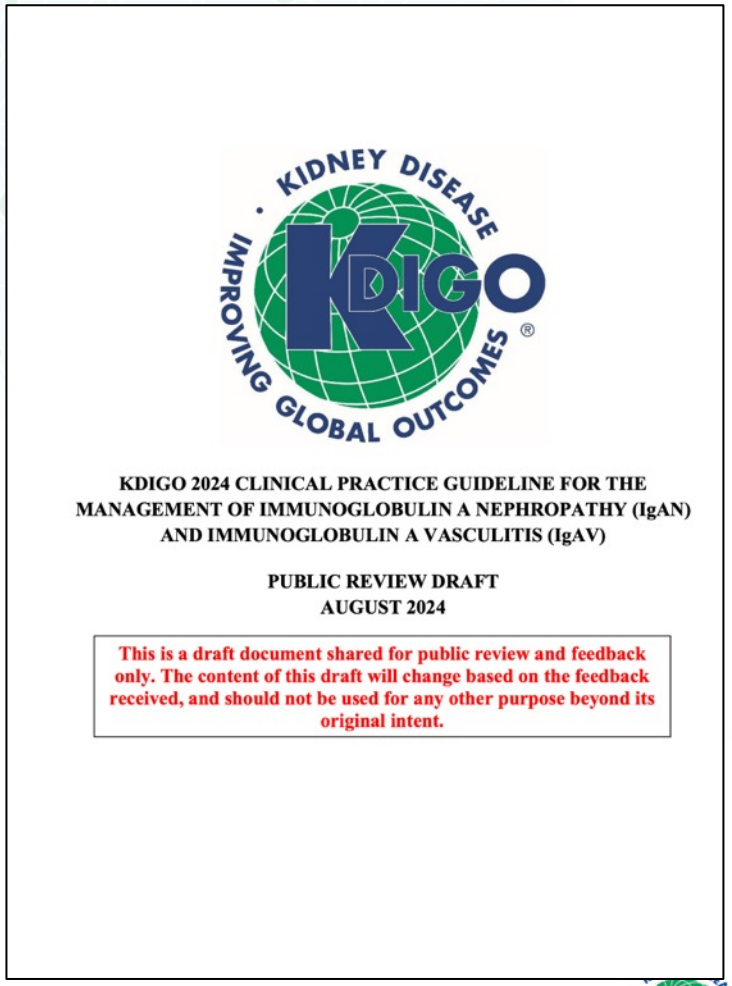
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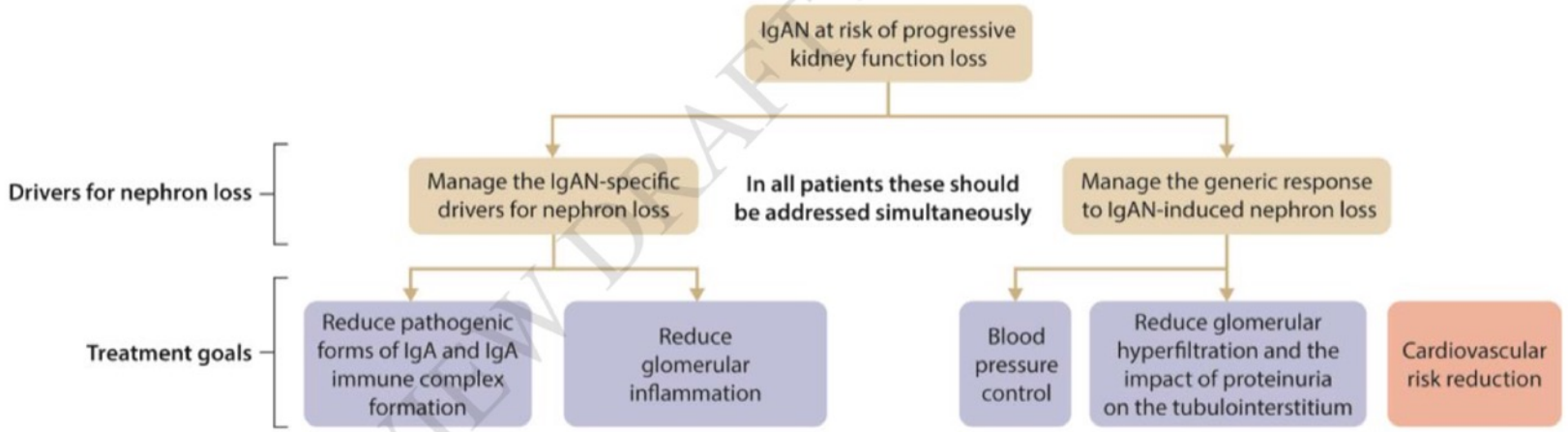
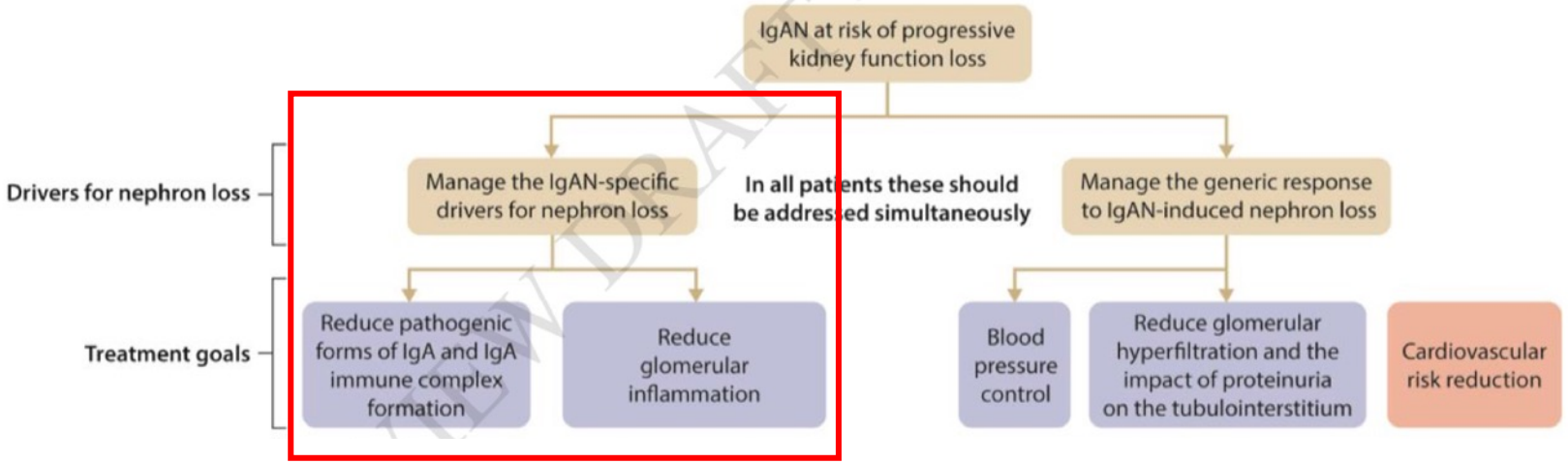


Figure 3 | Treatment targets in immunoglobulin A nephropathy (IgAN) and available to-date approved treatment options. *Measures to reduce glomerular hyperfiltration and the impact of proteinuria on the tubulointerstitium, using singly or in combination, renin-angiotensin system (RAS) blockade sparsentan, and sodium-glucose cotransporter-2 inhibition (SGLT2i). RASi, renin-angiotensin system inhibitors.



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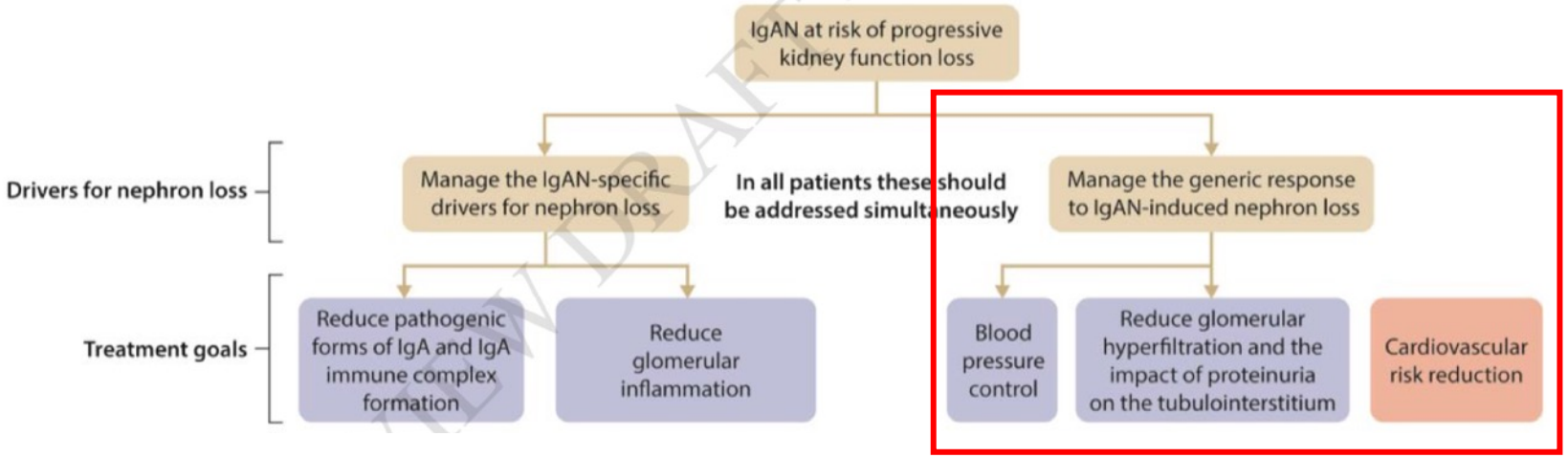

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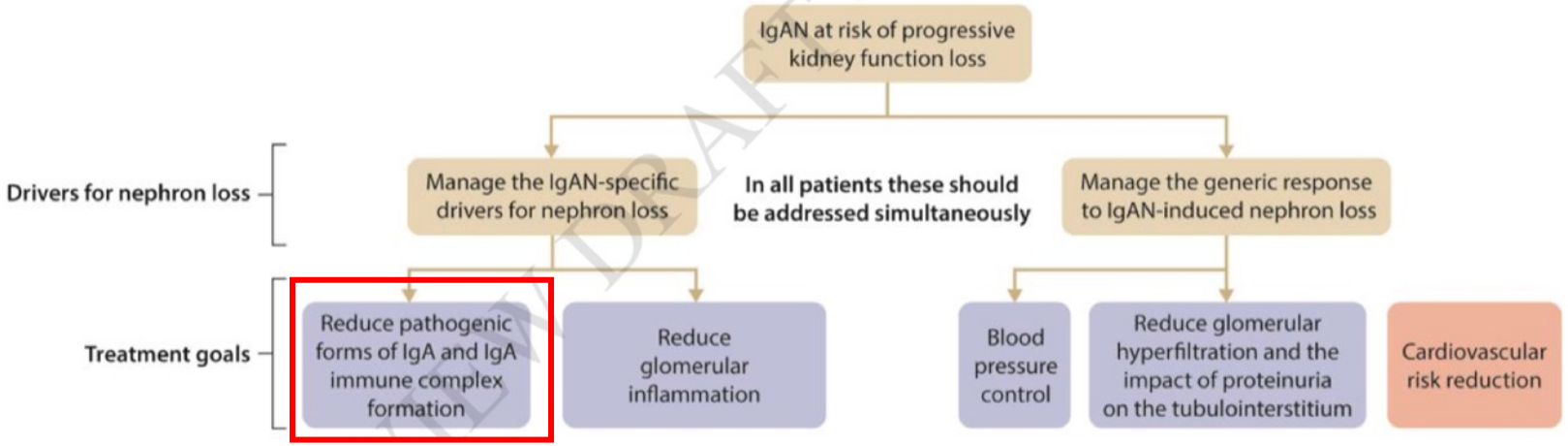

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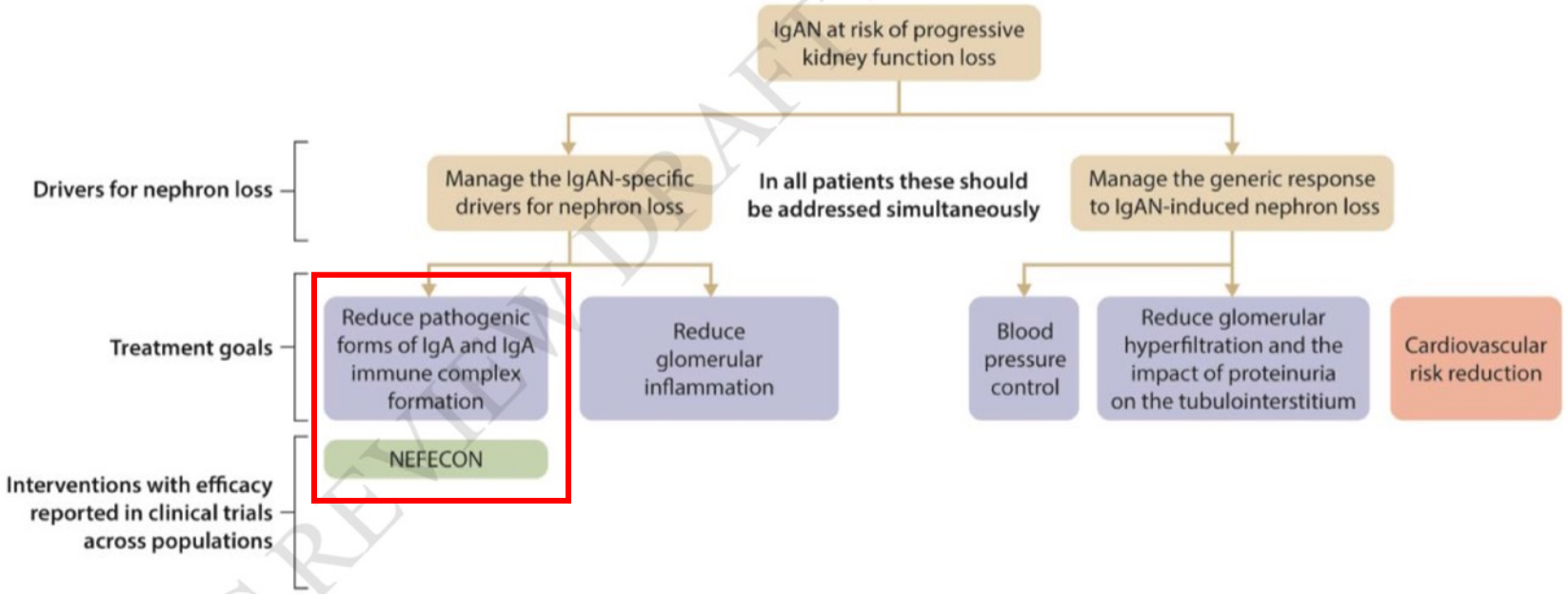

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2.3.3 Managing the IgAN-specific drivers for nephron loss

2.3.3.1 Reducing the production of pathogenic forms of IgA and IgA immune complex formation

Recommendation 2.3.3.1.1: We suggest treatment with a 9-month course of nefecon for patients who are at risk of progressive kidney function loss with IgAN *(2B)*.

Practice Point 2.3.3.1.1: Factors to consider before using nefecon in patients with IgAN

- **A single 9-month treatment course of nefecon is unlikely to produce a sustained clinical response in terms of proteinuria reduction or stabilization of eGFR and it is likely that many patients will need either repeated 9-month treatment cycles or a reduced-dose maintenance regimen**
- **The approval status, labelled indication and availability vary globally.**

Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial

Bengt C Fellström, Jonathan Barratt, Heather Cook, Rosanna Coppo, John Feehally, Johan W de Fijter, Jürgen Floege, Gerd Hetzel, Allan G Jardine, Francesco Locatelli, Bart D Maes, Alex Mercer, Fernando Ortiz, Manuel Praga, Søren S Sørensen, Vladimir Tesar, Lucia Del Vecchio, for the NEFIGAN Trial Investigators

Summary

Background IgA nephropathy is thought to be associated with mucosal immune system dysfunction, which manifests as renal IgA deposition that leads to impairment and end-stage renal disease in 20–40% of patients within 10–20 years. In this trial (NEFIGAN) we aimed to assess safety and efficacy of a novel targeted-release formulation of budesonide (TRF-budesonide), designed to deliver the drug to the distal ileum in patients with IgA nephropathy.

Methods We did a randomised, double-blind, placebo-controlled phase 2b trial, comprised of 6-month run-in, 9-month treatment, and 3-month follow-up phases at 62 nephrology clinics across ten European countries. We recruited patients aged at least 18 years with biopsy-confirmed primary IgA nephropathy and persistent proteinuria despite optimised renin-angiotensin system (RAS) blockade. We randomly allocated patients with a computer algorithm, with a fixed block size of three, in a 1:1:1 ratio to 16 mg/day TRF-budesonide, 8 mg/day TRF-budesonide, or placebo, stratified by baseline urine protein creatinine ratio (UPCR). Patients self-administered masked capsules, once daily, 1 h before breakfast during the treatment phase. All patients continued optimised RAS blockade treatment throughout the trial. Our primary outcome was mean change from baseline in UPCR for the 9-month treatment phase, which was assessed in the full analysis set, defined as all randomised patients who took at least one dose of trial medication and had at least one post-dose efficacy measurement. Safety was assessed in all patients who received the intervention. This trial is registered with ClinicalTrials.gov, number NCT01738035.

Findings Between Dec 11, 2012, and June 25, 2015, 150 randomised patients were treated (safety set) and 149 patients were eligible for the full analysis set. Overall, at 9 months TRF-budesonide (16 mg/day plus 8 mg/day) was associated with a 24·4% (SEM 7·7%) decrease from baseline in mean UPCR (change in UPCR vs placebo 0·74; 95% CI 0·59–0·94; p=0·0066). At 9 months, mean UPCR had decreased by 27·3% in 48 patients who received 16 mg/day (0·71; 0·53–0·94; p=0·0092) and 21·5% in the 51 patients who received 8 mg/day (0·76; 0·58–1·01; p=0·0290); 50 patients who received placebo had an increase in mean UPCR of 2·7%. The effect was sustained throughout follow-up. Incidence of adverse events was similar in all groups (43 [88%] of 49 in the TRF-budesonide 16 mg/day group, 48 [94%] of 51 in the TRF-budesonide 8 mg/day, and 42 [84%] of 50 controls). Two of 13 serious adverse events were possibly associated with TRF-budesonide—deep vein thrombosis (16 mg/day) and unexplained deterioration in renal function in follow-up (patients were tapered from 16 mg/day to 8 mg/day over 2 weeks and follow-up was assessed 4 weeks later).

Interpretation TRF-budesonide 16 mg/day, added to optimised RAS blockade, reduced proteinuria in patients with IgA nephropathy. This effect is indicative of a reduced risk of future progression to end-stage renal disease. TRF-budesonide could become the first specific treatment for IgA nephropathy targeting intestinal mucosal immunity upstream of disease manifestation.

Funding Pharmalink AB.

Introduction

Primary IgA nephropathy is the most prevalent chronic glomerular disease worldwide, with patients often diagnosed as young adults.[1] About 20–40% of patients progress to end-stage renal disease within 20–20 years of diagnosis.[2–4] Major risk factors for progression to end-stage renal disease are persistent proteinuria, hypertension, and reduced glomerular filtration rate (GFR).[2,3,5] Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for glomerulonephritis recommend renin-angiotensin system (RAS) blockade with angiotensin-converting-enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) as first-line treatment for patients with IgA nephropathy with proteinuria of more than 1 g/day (recommendation level 1B), and suggest up-titration as far as tolerated to the maximum recommended dose to achieve proteinuria of less than 1 g/day (recommendation level 2D). For patients with persistent proteinuria of more than 1 g/day and GFR greater than 50 mL/min per 1·73 m² despite 6 months' optimised RAS blockade, KDIGO

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Results from part A of the multi-center, double-blind, randomized, placebo-controlled NeflgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy

see commentary on page 258

OPEN

Jonathan Barratt[1], Richard Lafayette[2], Jens Kristensen[3], Andrew Stone[4], Daniel Cattran[5], Jürgen Floege[6], Vladimir Tesar[7], Hernán Trimarchi[8], Hong Zhang[9], Necmi Eren[10], Alexander Paliege[11] and Brad H. Rovin[12]; for the NeflgArd Trial Investigators[13]

[1]College of Medicine Biological Sciences and Psychology, University of Leicester, Leicester, UK; [2]Division of Nephrology, Department of Medicine, Stanford University, Stanford, California, USA; [3]Calliditas Therapeutics AB, Stockholm, Sweden; [4]Stone Biostatistics Ltd., Crewe, UK; [5]Division of Nephrology, Toronto General Hospital Research Institute, University of Toronto, Toronto, Ontario, Canada; [6]Department of Nephrology and Clinical Immunology, Rheinisch Westfälische Technische Hochschule Aachen University Hospital, Aachen, Germany; [7]Department of Nephrology, 1st School of Medicine and General University Hospital, Charles University, Prague, Czech Republic; [8]Nephrology Service, Hospital Británico de Buenos Aires, Buenos Aires, Argentina; [9]Renal Division, Peking University First Hospital, Peking University Institute of Nephrology, Beijing, China; [10]Department of Nephrology, Kocaeli University, Kocaeli, Turkey; [11]Division of Nephrology, Department of Internal Medicine III, University Hospital Carl Gustav Carus at the Technische Universität Dresden, Dresden, Germany; and [12]Division of Nephrology, the Ohio State University Wexner Medical Center, Columbus, Ohio, USA

The therapeutic potential of a novel, targeted-release formulation of oral budesonide (Nefecon) for the treatment of IgA nephropathy (IgAN) was first demonstrated by the phase 2b NEFIGAN trial. To verify these findings, the phase 3 NefigArd trial tested the efficacy and safety of nine months of treatment with Nefecon (16 mg/d) versus placebo in adult patients with primary IgAN at risk of progressing to kidney failure (ClinicalTrials.gov: NCT03643965). NeflgArd was a multicenter, randomized, double-blind, placebo-controlled two-part trial. In Part A, 199 patients with IgAN were treated with Nefecon or placebo for nine months and observed for an additional three months. The primary endpoint for Part A was 24-hour urine protein-to-creatinine ratio (UPCR) after nine months. Secondary efficacy outcomes evaluated included estimated glomerular filtration rate (eGFR) at nine and 12 months and the UPCR at 12 months. At nine months, UPCR was 27% lower in the Nefecon group compared with placebo, along with a benefit in eGFR preservation corresponding to a 3.87 ml/min/1.73 m² difference versus placebo (both significant). Nefecon was well-tolerated, and treatment-emergent adverse events were mostly mild to moderate in severity and reversible. Part B is ongoing and will be reported on later. Thus, NeflgArd is the first phase 3 IgA nephropathy trial to show clinically important improvements in UPCR and eGFR and confirms the findings from the phase 2b NEFIGAN study.

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KEYWORDS: glomerular disease; glucocorticoids; gut-associated lymphoid tissue; IgA nephropathy

IgA nephropathy (IgAN) is a mesangioproliferative glomerulonephritis, characterized by the deposition of galactose-deficient IgA1 (Gd-IgA1)–containing immune complexes in the glomerular mesangium.[1] These immune complexes initiate a cascade of inflammatory events, eventually causing irreversible glomerulosclerosis and tubulointerstitial inflammation and fibrosis with loss of kidney function; in patients with progressive disease (i.e., proteinuria >1 g/24 h), the risk of kidney failure may be up to 50% within 20 years.[2–5] At the time the present study was initiated, no IgAN-specific treatments were available, and guidelines recommended goal-directed supportive care comprising lifestyle change, optimal blood pressure control, and renin-angiotensin system (RAS) blockade to reduce proteinuria.[5–8]

There is accumulating evidence for the gut mucosal immune system and mucosal-derived Gd-IgA1 in the pathogenesis of primary IgAN. Peyer's patches are aggregations of lymphoid follicles, located in the mucosal layer of the intestine, and concentrated in the ileum. They are part of the gut-associated lymphoid system and serve as antigen sampling

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[13]The NeflgArd Trial Investigators are listed in the Appendix.

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Efficacy and safety of a targeted-release formulation of budesonide in patients with primary IgA nephropathy (NeflgArd): 2-year results from a randomised phase 3 trial

Richard Lafayette, Jens Kristensen, Andrew Stone, Jürgen Floege, Vladimir Tesař, Hernán Trimarchi, Hong Zhang, Necmi Eren, Alexander Paliege, Heather N Reich, Brad H Rovin, Jonathan Barratt, on behalf of the NeflgArd trial investigators

Summary

Background IgA nephropathy is a chronic immune-mediated kidney disease and a major cause of kidney failure worldwide. The gut mucosal immune system is implicated in its pathogenesis, and Nefecon is a novel, oral, targeted-release formulation of budesonide designed to act at the gut mucosal level. We present findings from the 2-year, phase 3 NeflgArd trial of Nefecon in patients with IgA nephropathy.

Methods In this phase 3, multicentre, randomised, double-blind, placebo-controlled trial, adult patients (aged ≥18 years) with primary IgA nephropathy, estimated glomerular filtration rate (eGFR) 35–90 mL/min per 1·73 m², and persistent proteinuria (urine protein–creatinine ratio ≥0·8 g/g or proteinuria ≥1 g/24 h) despite optimised renin-angiotensin system blockade were enrolled at 132 hospital-based clinical sites in 20 countries worldwide. Patients were randomly assigned (1:1) to receive 16 mg/day oral capsules of Nefecon or matching placebo for 9 months, followed by a 15-month observational follow-up period off study drug. Randomisation via an interactive response technology system was stratified according to baseline proteinuria (<2 or ≥2 g/24 h), baseline eGFR (<60 or ≥60 mL/min per 1·73 m²), and region (Asia-Pacific, Europe, North America, or South America). Patients, investigators, and site staff were masked to treatment assignment throughout the 2-year trial. Optimised supportive care was also continued throughout the trial. The primary efficacy endpoint was time-weighted average of eGFR over 2 years. Efficacy and safety analyses were done in the full analysis set (ie, all randomly assigned patients). The trial was registered on ClinicalTrials.gov, NCT03643965, and is completed.

Findings Patients were recruited to the NeflgArd trial between Sept 5, 2018, and Jan 20, 2021, with 364 patients (182 per treatment group) randomly assigned in the full analysis set. 240 (66%) patients were men and 124 (34%) were women, and 275 (76%) identified as White. The time-weighted average of eGFR over 2 years showed a statistically significant treatment benefit with Nefecon versus placebo (difference 5·05 mL/min per 1·73 m² [95% CI 3·24 to 7·38], p<0·0001), with a time-weighted average change of −2·47 mL/min per 1·73 m² (95% CI −3·88 to −1·02) reported with Nefecon and −7·52 mL/min per 1·73 m² (−8·83 to −6·18) reported with placebo. The most commonly reported treatment-emergent adverse events during treatment with Nefecon were peripheral oedema (31 [17%] patients, vs placebo, seven [4%] patients), hypertension (22 [12%] vs six [3%]), muscle spasms (22 [12%] vs seven [4%]), acne (20 [11%] vs two [1%]), and headache (19 [10%] vs 14 [8%]). No treatment-related deaths were reported.

Interpretation A 9-month treatment period with Nefecon provided a clinically relevant reduction in eGFR decline and a durable reduction in proteinuria versus placebo, providing support for a disease-modifying effect in patients with IgA nephropathy. Nefecon was also well tolerated, with a safety profile as expected for a locally acting oral budesonide product.

Funding Calliditas Therapeutics.

Introduction

IgA nephropathy is a chronic immune-mediated kidney disease characterised by IgA deposition in the glomeruli.[1] IgA nephropathy is the most common primary glomerular disease globally and has serious consequences, including reduced life expectancy; most patients with IgA nephropathy are expected to develop kidney failure, with up to 50% doing so within 20 years of presentation.[2–4] Therefore, IgA nephropathy places a substantial burden on patients and health-care services worldwide. With no cure for IgA nephropathy, current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, published in 2021, recommend providing optimised supportive care (blood pressure management, lifestyle modification, maximally tolerated renin-angiotensin system [RAS] inhibition to reduce proteinuria, and addressing cardiovascular risk).[5] After supportive care, patients who remain at high risk for progressive chronic kidney disease should be considered for a clinical trial, or for systemic glucocorticoids (if they

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Targeted-release budesonide modifies key pathogenic biomarkers in immunoglobulin A nephropathy: insights from the NEFIGAN trial

OPEN

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KEYWORDS: chronic kidney disease; complement; cytokines; glomerulus; IgA nephropathy; proteinuria

Nefecon is the first approved treatment for patients with immunoglobulin A nephropathy (IgAN) at high risk of progression to kidney failure (accelerated approval: US Food and Drug Administration; conditional approval: European Medicines Agency).[1–3] Nefecon delivers budesonide, in a targeted formulation, to the gut-associated lymphoid tissue (GALT) of the ileum directly addressing immune dysregulation within this Peyer's patches–rich area of the GALT and downregulating the local production of the polymeric poorly O-galactosylated form of IgA1 or galactose-deficient IgA1 (Gd-IgA1) and generation of pathogenic IgA-containing immune complexes (IgA-IC).[2] The aim of the current analysis is to explore the biochemical pathways through which Nefecon exerted its effects in patients treated in the NEFIGAN study.

METHODS

NEFIGAN (ClinicalTrials.gov: NCT01738035) was a randomized, double-blind, placebo-controlled, phase 2b trial to assess the safety and efficacy of Nefecon in patients (≥18 years) with IgAN and overt proteinuria despite optimized renin-angiotensin-aldosterone system blockade therapy.[2] Patients (n = 150) were stratified according to the baseline urine protein creatinine ratio (≤0.9 g/g and >0.9 g/g) and were randomized (1:1:1) to Nefecon 8 mg/d, Nefecon 16 mg/d, or placebo. After a 6-month run-in phase, patients underwent a 9-month treatment phase followed by a 3-month follow-up phase. Blood and urine samples were collected during the trial and exploratory analyses of a range of IgAN-related biomarkers were conducted, using in-house enzyme-linked immunosorbent assays, commercial enzyme-linked immunosorbent assay duo kits, and multiplex immunoassays. A full description of the methods is provided in Supplementary Methods. All ELISAs are listed in Supplementary Table S1, and the Luminex assays used for the biomarker analyses are shown in Supplementary Table S2.

RESULTS

Patient demographics and baseline characteristics are given in Supplementary Table S3.[4] Changes from baseline in multiple biomarkers were observed at 9 months, as described below,

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Background IgA nephropathy is thought to be associated with mucosal immune system dysfunction, which manifests as renal IgA deposition that leads to impairment and end-stage renal disease in 20–40% of patients within 10–20 years. In this trial (NEFIGAN) we aimed to assess safety and efficacy of a novel targeted-release formulation of budesonide (TRF-budesonide), designed to deliver the drug to the distal ileum in patients with IgA nephropathy.

Methods We did a randomised, double-blind, placebo-controlled phase 2b trial, comprised of 6-month run-in, 9-month treatment, and 3-month follow-up phases at 62 nephrology clinics across ten European countries. We recruited patients aged at least 18 years with biopsy-confirmed primary IgA nephropathy and persistent proteinuria despite optimised renin-angiotensin system (RAS) blockade. We randomly allocated patients with a computer algorithm, with a fixed block size of three, in a 1:1:1 ratio to 16 mg/day TRF-budesonide, 8 mg/day TRF-budesonide, or placebo, stratified by baseline urine protein creatinine ratio (UPCR). Patients self-administered masked capsules, once daily, 1 h before breakfast during the treatment phase. All patients continued optimised RAS blockade treatment throughout the trial. Our primary outcome was mean change from baseline in UPCR for the 9-month treatment phase, which was assessed in the full analysis set, defined as all randomised patients who took at least one dose of trial medication and had at least one post-dose efficacy measurement. Safety was assessed in all patients who received the intervention. This trial is registered with ClinicalTrials.gov, number NCT01738035.

Findings Between Dec 11, 2012, and June 25, 2015, 150 randomised patients were treated (safety set) and 149 patients were eligible for the full analysis set. Overall, at 9 months TRF-budesonide (16 mg/day plus 8 mg/day) was associated with a 24·4% (SEM 7·7%) decrease from baseline in mean UPCR (change in UPCR vs placebo 0·74; 95% CI 0·59–0·94; p=0·0066). At 9 months, mean UPCR had decreased by 27·3% in 48 patients who received 16 mg/day (0·71; 0·53–0·94; p=0·0092) and 21·5% in the 51 patients who received 8 mg/day (0·76; 0·58–1·01; p=0·0290); 50 patients who received placebo had an increase in mean UPCR of 2·7%. The effect was sustained throughout follow-up. Incidence of adverse events was similar in all groups (43 [88%] of 49 in the TRF-budesonide 16 mg/day group, 48 [94%] of 51 in the TRF-budesonide 8 mg/day, and 42 [84%] of 50 controls). Two of 13 serious adverse events were possibly associated with TRF-budesonide—deep vein thrombosis (16 mg/day) and unexplained deterioration in renal function in follow-up (patients were tapered from 16 mg/day to 8 mg/day over 2 weeks and follow-up was assessed 4 weeks later).

Interpretation TRF-budesonide 16 mg/day, added to optimised RAS blockade, reduced proteinuria in patients with IgA nephropathy. This effect is indicative of a reduced risk of future progression to end-stage renal disease. TRF-budesonide could become the first specific treatment for IgA nephropathy targeting intestinal mucosal immunity upstream of disease manifestation.

Funding Pharmalink AB.

Introduction

Primary IgA nephropathy is the most prevalent chronic glomerular disease worldwide, with patients often diagnosed as young adults.[1] About 20–40% of patients progress to end-stage renal disease within 10–20 years of diagnosis.[2–4] Major risk factors for progression to end-stage renal disease are persistent proteinuria, hypertension, and reduced glomerular filtration rate (GFR).[2,3,5] Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for glomerulonephritis recommend renin-angiotensin system (RAS) blockade with angiotensin-converting-enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) as first-line treatment for patients with IgA nephropathy with proteinuria of more than 1 g/day (recommendation level 1B), and suggest up-titration as far as tolerated to the maximum recommended dose to achieve proteinuria of less than 1 g/day (recommendation level 2D). For patients with persistent proteinuria of more than 1 g/day and GFR greater than 50 mL/min per 1·73 m² despite 6 months' optimised RAS blockade, KDIGO

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Results from part A of the multi-center, double-blind, randomized, placebo-controlled NefIgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy

see commentary on page 258

OPEN

Jonathan Barratt[1], Richard Lafayette[2], Jens Kristensen[3], Andrew Stone[4], Daniel Cattran[5], Jürgen Floege[6], Vladimir Tesar[7], Hernán Trimarchi[8], Hong Zhang[9], Necmi Eren[10], Alexander Paliege[11] and Brad H. Rovin[12]; for the NefIgArd Trial Investigators[13]

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The therapeutic potential of a novel, targeted-release formulation of oral budesonide (Nefecon) for the treatment of IgA nephropathy (IgAN) was first demonstrated by the phase 2b NEFIGAN trial. To verify these findings, the phase 3 NefIgArd trial tested the efficacy and safety of nine months of treatment with Nefecon (16 mg/d) versus placebo in adult patients with primary IgAN at risk of progressing to kidney failure (ClinicalTrials.gov: NCT03643965). NefIgArd was a multicenter, randomized, double-blind, placebo-controlled two-part trial. In Part A, 199 patients with IgAN were treated with Nefecon or placebo for nine months and observed for an additional three months. The primary endpoint for Part A was 24-hour urine protein-to-creatinine ratio (UPCR) after nine months. Secondary efficacy outcomes evaluated included estimated glomerular filtration rate (eGFR) at nine and 12 months and the UPCR at 12 months. At nine months, UPCR was 27% lower in the Nefecon group compared with placebo, along with a benefit in eGFR preservation corresponding to a 3.87 ml/min/1.73 m² difference versus placebo (both significant). Nefecon was well-tolerated, and treatment-emergent adverse events were mostly mild to moderate in severity and reversible. Part B is ongoing and will be reported on later. Thus, NefIgArd is the first phase 3 IgA nephropathy trial to show clinically important improvements in UPCR and eGFR and confirms the findings from the phase 2b NEFIGAN study.

Kidney International (2023) **103**, 391–402; https://doi.org/10.1016/j.kint.2022.09.017

KEYWORDS: glomerular disease; glucocorticoids; gut-associated lymphoid tissue; IgA nephropathy

IgA nephropathy (IgAN) is a mesangioproliferative glomerulonephritis, characterized by the deposition of galactose-deficient IgA1 (Gd-IgA1)–containing immune complexes in the glomerular mesangium.[1] These immune complexes initiate a cascade of inflammatory events, eventually causing irreversible glomerulosclerosis and tubulointerstitial inflammation and fibrosis with loss of kidney function; in patients with progressive disease (i.e., proteinuria >1 g/24 h), the risk of kidney failure may be up to 50% within 20 years.[2–5] At the time the present study was initiated, no IgAN-specific treatments were available, and guidelines recommended goal-directed supportive care comprising lifestyle change, optimal blood pressure control, and renin-angiotensin system (RAS) blockade to reduce proteinuria.[5–8]

There is accumulating evidence for the gut mucosal immune system and mucosal-derived Gd-IgA1 in the pathogenesis of primary IgAN. Peyer's patches are aggregations of lymphoid follicles, located in the mucosal layer of the intestine, and concentrated in the ileum. They are part of the gut-associated lymphoid system and serve as antigen sampling

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[13]The NefIgArd Trial Investigators are listed in the Appendix.

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Efficacy and safety of a targeted-release formulation of budesonide in patients with primary IgA nephropathy (NefIgArd): 2-year results from a randomised phase 3 trial

Richard Lafayette, Jens Kristensen, Andrew Stone, Jürgen Floege, Vladimir Tesař, Hernán Trimarchi, Hong Zhang, Necmi Eren, Alexander Paliege, Heather N Reich, Brad H Rovin, Jonathan Barratt, *on behalf of the NefIgArd trial investigators*

Summary

Background IgA nephropathy is a chronic immune-mediated kidney disease and a major cause of kidney failure worldwide. The gut mucosal immune system is implicated in its pathogenesis, and Nefecon is a novel, oral, targeted-release formulation of budesonide designed to act at the gut mucosal level. We present findings from the 2-year, phase 3 NefIgArd trial of Nefecon in patients with IgA nephropathy.

Methods In this phase 3, multicentre, randomised, double-blind, placebo-controlled trial, adult patients (aged ≥18 years) with primary IgA nephropathy, estimated glomerular filtration rate (eGFR) 35–90 mL/min per 1·73 m², and persistent proteinuria (urine protein–creatinine ratio ≥0·8 g/g or proteinuria ≥1 g/24 h) despite optimised renin-angiotensin system blockade were enrolled at 132 hospital-based clinical sites in 20 countries worldwide. Patients were randomly assigned (1:1) to receive 16 mg/day oral capsules of Nefecon or matching placebo for 9 months, followed by a 15-month observational follow-up period off study drug. Randomisation via an interactive response technology system was stratified according to baseline proteinuria (<2 or ≥2 g/24 h), baseline eGFR (<60 or ≥60 mL/min per 1·73 m²), and region (Asia-Pacific, Europe, North America, or South America). Patients, investigators, and site staff were masked to treatment assignment throughout the 2-year trial. Optimised supportive care was also continued throughout the trial. The primary efficacy endpoint was time-weighted average of eGFR over 2 years. Efficacy and safety analyses were done in the full analysis set (ie, all randomly assigned patients). The trial was registered on ClinicalTrials.gov, NCT03643965, and is completed.

Findings Patients were recruited to the NefIgArd trial between Sept 5, 2018, and Jan 20, 2021, with 364 patients (182 per treatment group) randomly assigned in the full analysis set. 240 (66%) patients were men and 124 (34%) were women, and 275 (76%) identified as White. The time-weighted average of eGFR over 2 years showed a statistically significant treatment benefit with Nefecon versus placebo (difference 5·05 mL/min per 1·73 m² [95% CI 3·24 to 7·38], p<0·0001), with a time-weighted average change of −2·47 mL/min per 1·73 m² (95% CI −3·88 to −1·02) reported with Nefecon and −7·52 mL/min per 1·73 m² (−8·83 to −6·18) reported with placebo. The most commonly reported treatment-emergent adverse events during treatment with Nefecon were peripheral oedema (31 [17%] patients, vs placebo, seven [4%] patients), hypertension (22 [12%] vs six [3%]), muscle spasms (22 [12%] vs seven [4%]), acne (20 [11%] vs two [1%]), and headache (19 [10%] vs 14 [8%]). No treatment-related deaths were reported.

Interpretation A 9-month treatment period with Nefecon provided a clinically relevant reduction in eGFR decline and a durable reduction in proteinuria versus placebo, providing support for a disease-modifying effect in patients with IgA nephropathy. Nefecon was also well tolerated, with a safety profile as expected for a locally acting oral budesonide product.

Funding Calliditas Therapeutics.

Introduction

IgA nephropathy is a chronic immune-mediated kidney disease characterised by IgA deposition in the glomeruli.[1] IgA nephropathy is the most common primary glomerular disease globally and has serious consequences, including reduced life expectancy; most patients with IgA nephropathy are expected to develop kidney failure, with up to 50% doing so within 20 years of presentation.[2–5] Therefore, IgA nephropathy places a substantial burden on patients and health-care services worldwide. With no cure for IgA nephropathy, current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, published in 2021, recommend providing optimised supportive care (blood pressure management, lifestyle modification, maximally tolerated renin-angiotensin system [RAS] inhibition to reduce proteinuria, and addressing cardiovascular risk).[1] After supportive care, patients who remain at high risk for progressive chronic kidney disease should be considered for a clinical trial, or for systemic glucocorticoids (if they

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Targeted-release budesonide modifies key pathogenic biomarkers in immunoglobulin A nephropathy: insights from the NEFIGAN trial

OPEN

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KEYWORDS: chronic kidney disease; complement; cytokines; glomerulus; IgA nephropathy; proteinuria

Nefecon is the first approved treatment for patients with immunoglobulin A nephropathy (IgAN) at high risk of progression to kidney failure (accelerated approval: US Food and Drug Administration; conditional approval: European Medicines Agency).[1–3] Nefecon delivers budesonide, in a targeted formulation, to the gut-associated lymphoid tissue (GALT) of the ileum directly addressing immune dysregulation within this Peyer's patches–rich area of the GALT and downregulating the local production of the polymeric poorly O-galactosylated form of IgA1 or galactose-deficient IgA1 (Gd-IgA1) and generation of pathogenic IgA-containing immune complexes (IgA-IC).[2] The aim of the current analysis is to explore the biochemical pathways through which Nefecon exerted its effects in patients treated in the NEFIGAN study.

METHODS

NEFIGAN (ClinicalTrials.gov: NCT01738035) was a randomized, double-blind, placebo-controlled, phase 2b trial to assess the safety and efficacy of Nefecon in patients (≥18 years) with IgAN and overt proteinuria despite optimized renin-angiotensin-aldosterone system blockade therapy.[2] Patients (n = 150) were stratified according to the baseline urine protein creatinine ratio (≤0.9 g/g and >0.9 g/g) and were randomized (1:1:1) to Nefecon 8 mg/d, Nefecon 16 mg/d, or placebo. After a 6-month run-in phase, patients underwent a 9-month treatment phase followed by a 3-month follow-up phase. Blood and urine samples were collected during the trial and exploratory analyses of a range of IgAN-related biomarkers were conducted, using in-house enzyme-linked immunosorbent assays, commercial enzyme-linked immunosorbent assay duo kits, and multiplex immunoassays. A full description of the methods is provided in Supplementary Methods. All ELISAs are listed in Supplementary Table S1, and the Luminex assays used for the biomarker analyses are shown in Supplementary Table S2.

RESULTS

Patient demographics and baseline characteristics are given in Supplementary Table S3.[3] Changes from baseline in multiple biomarkers were observed at 9 months, as described below,

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[8]DW, MM, and BF are joint first authors.

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2.3.3 Managing the IgAN-specific drivers for nephron loss

2.3.3.1 Reducing the production of pathogenic forms of IgA and IgA immune complex formation

Recommendation 2.3.3.1.1: We suggest treatment with a 9-month course of nefecon for patients who are at risk of progressive kidney function loss with IgAN *(2B)*.

Practice Point 2.3.3.1.1: Factors to consider before using nefecon in patients with IgAN

- **A single 9-month treatment course of nefecon is unlikely to produce a sustained clinical response in terms of proteinuria reduction or stabilization of eGFR and it is likely that many patients will need either repeated 9-month treatment cycles or a reduced-dose maintenance regimen**
- **The approval status, labelled indication and availability vary globally.**

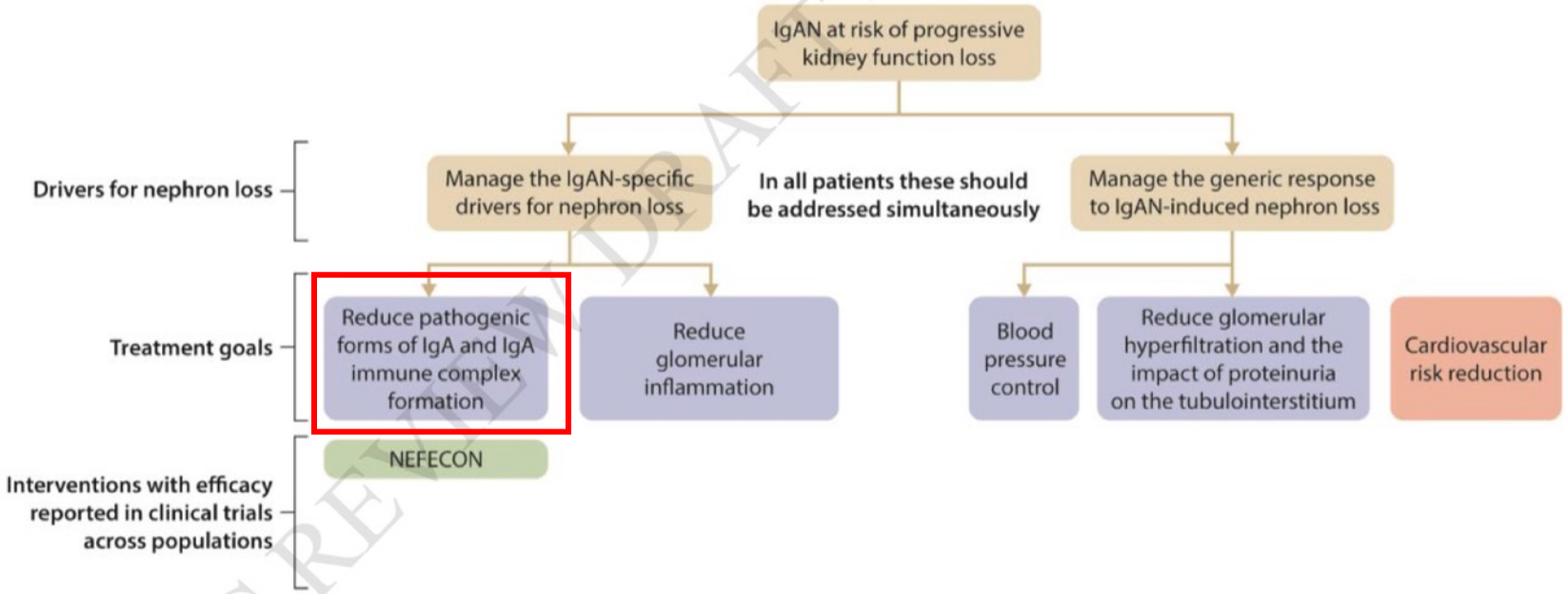
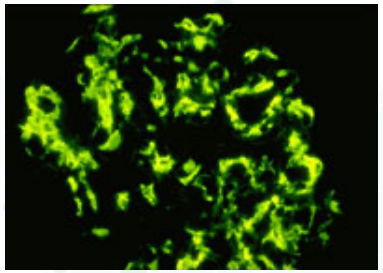


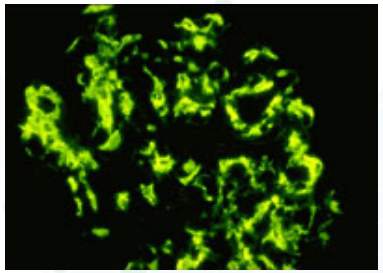
Figure 3 | Treatment targets in immunoglobulin A nephropathy (IgAN) and available to-date approved treatment options. *Measures to reduce glomerular hyperfiltration and the impact of proteinuria on the tubulointerstitium, using singly or in combination, renin-angiotensin system (RAS) blockade sparsentan, and sodium-glucose cotransporter-2 inhibition (SGLT2i). RASi, renin-angiotensin system inhibitors.

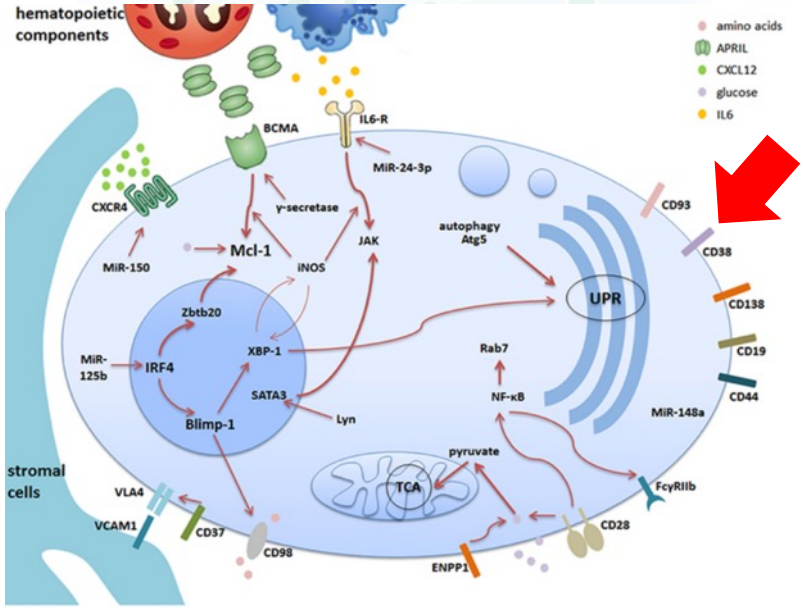


Pathogenic IgA Synthesis

B cell depletion

B cell modulation





Pathogenic IgA Synthesis

B cell depletion

B cell modulation

ACTIVE, NOT RECRUITING

Clinical Trial to Assess Efficacy and Safety of the Human Anti-CD38 Antibody Felzartamab (MOR202) in IgA Nephropathy (IGNAZ)

ClinicalTrials.gov ID NCT05065970

Sponsor HI-Bio

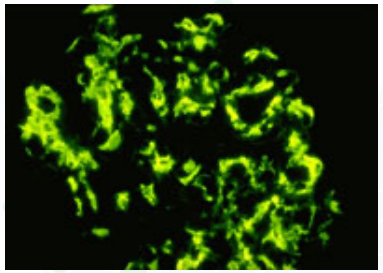
Information provided by HI-Bio (Responsible Party)

Last Update Posted 2024-02-06

TAK-079-1006 RECRUITMENT COMPLETE

A Study of Mezagitamab in Adults With Primary Immunoglobulin A Nephropathy Receiving Stable Background Therapy

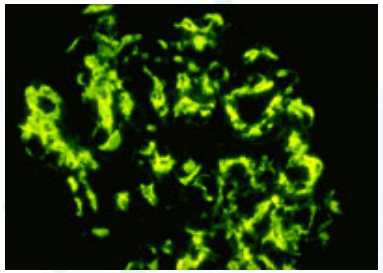
Clinicaltrials.gov #NCT05174221 | EudraCT #2021-005023-20 | jRCT #jRCT2011220009



Pathogenic IgA Synthesis

B cell depletion

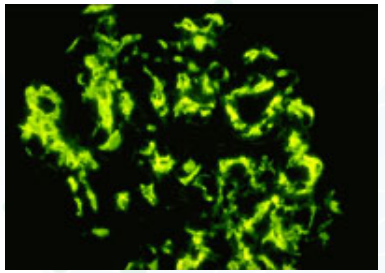
B cell modulation



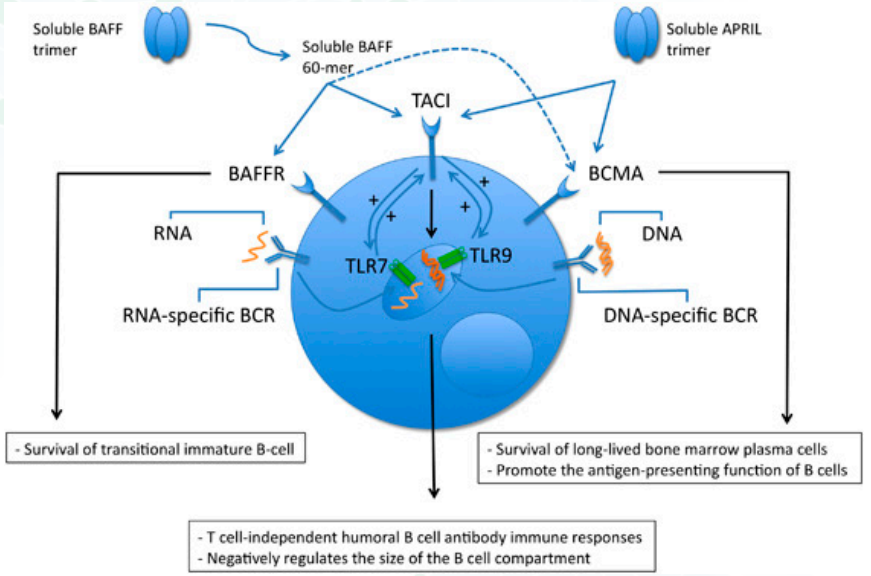
Pathogenic IgA Synthesis

B cell depletion

B cell modulation

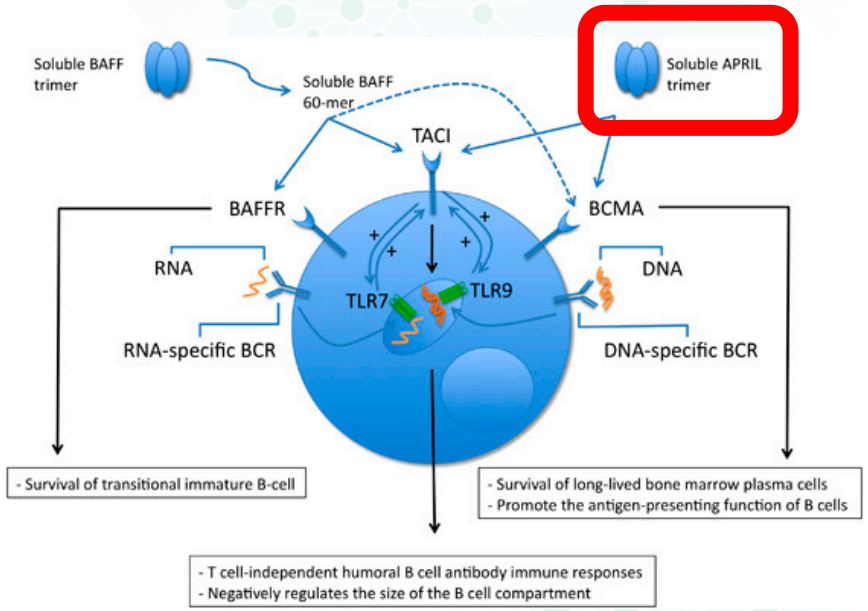


Pathogenic IgA Synthesis



B cell depletion

B cell modulation



ACTIVE, NOT RECRUITING

Visionary Study: Phase 3 Trial of Sibeprenlimab in Immunoglobulin A Nephropathy (IgAN)

ClinicalTrials.gov ID NCT05248646

Sponsor Otsuka Pharmaceutical Development & Commercialization, Inc.

Information provided by Otsuka Pharmaceutical Development & Commercialization, Inc. (Responsible Party)

Last Update Posted 2024-03-26

RECRUITING

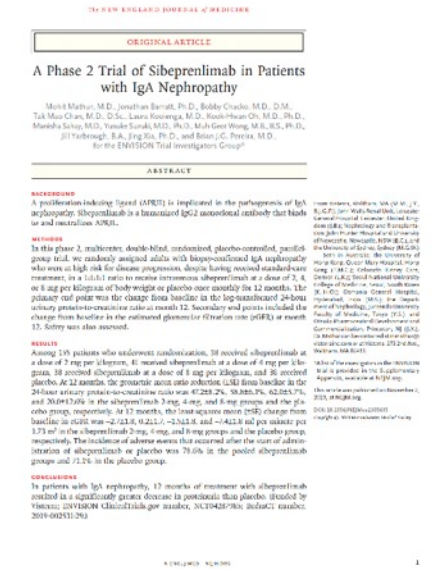
A Study of BION-1301 in Adults With IgA Nephropathy

ClinicalTrials.gov ID NCT05852938

Sponsor Chinook Therapeutics, Inc.

Information provided by Chinook Therapeutics, Inc. (Responsible Party)

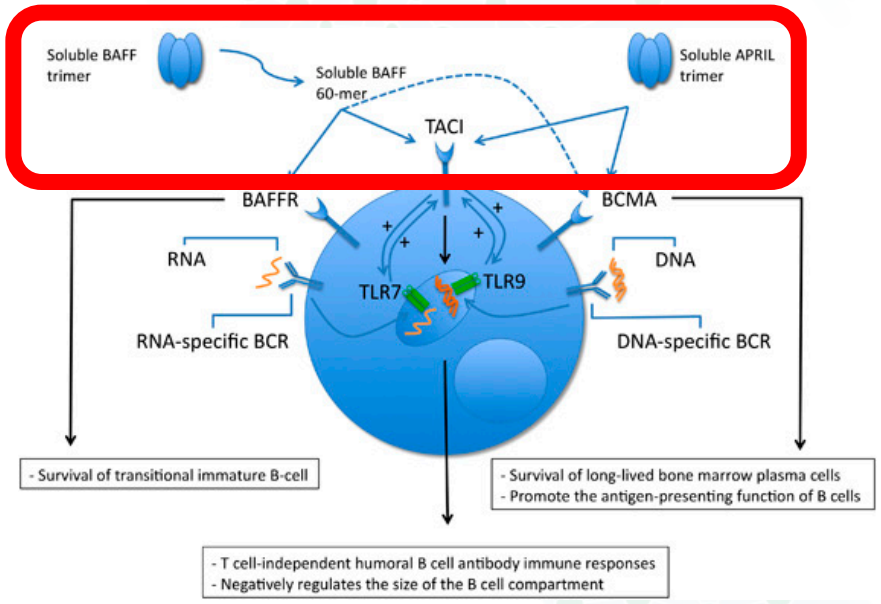
Last Update Posted 2024-04-19



ORIGINAL ARTICLE

A Phase 2 Trial of Sibeprenlimab in Patients with IgA Nephropathy

ABSTRACT



RECRUITING

Atacicept in Subjects With IgA Nephropathy (ORIGIN 3)

ClinicalTrials.gov ID NCT04716231

Sponsor Vera Therapeutics, Inc.

Information provided by Vera Therapeutics, Inc. (Responsible Party)

Last Update Posted 2023-11-29

RECRUITING

A Study of Telitacicept in Patients With Primary IgA Nephropathy

ClinicalTrials.gov ID NCT05799287

Sponsor RemeGen Co., Ltd.

Information provided by RemeGen Co., Ltd. (Responsible Party)

Last Update Posted 2023-09-06

Recruiting

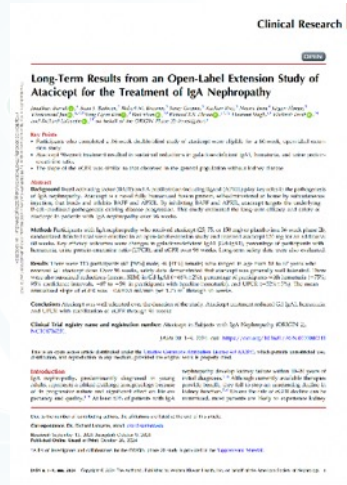
Evaluation of Efficacy of Povetacicept in Adults With Immunoglobulin A Nephropathy (IgAN)

ClinicalTrials.gov ID NCT06564142

Sponsor Alpine Immune Sciences Inc, A Subsidiary of Vertex

Information provided by Alpine Immune Sciences, Inc. (Alpine Immune Sciences Inc, A Subsidiary of Vertex) (Responsible Party)

Last Update Posted 2024-12-05



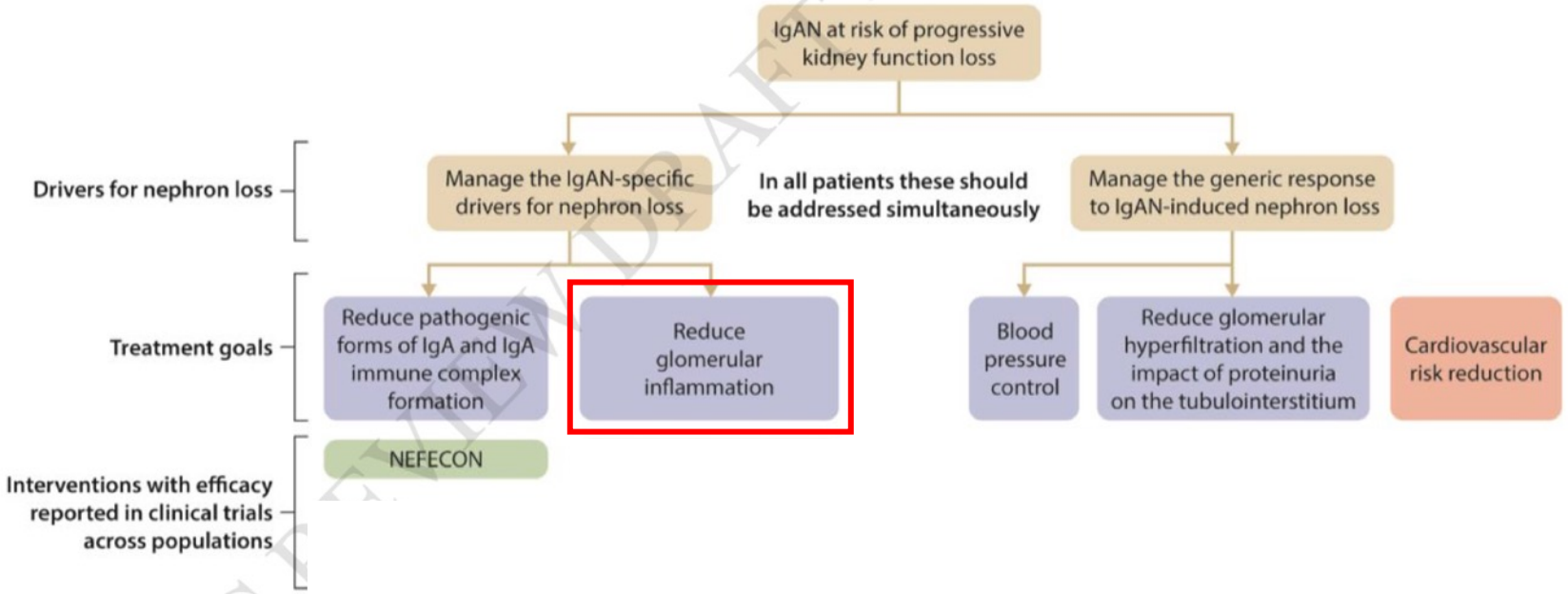


Figure 3 | Treatment targets in immunoglobulin A nephropathy (IgAN) and available to-date approved treatment options. *Measures to reduce glomerular hyperfiltration and the impact of proteinuria on the tubulointerstitium, using singly or in combination, renin-angiotensin system (RAS) blockade sparsentan, and sodium-glucose cotransporter-2 inhibition (SGLT2i). RASi, renin-angiotensin system inhibitors.

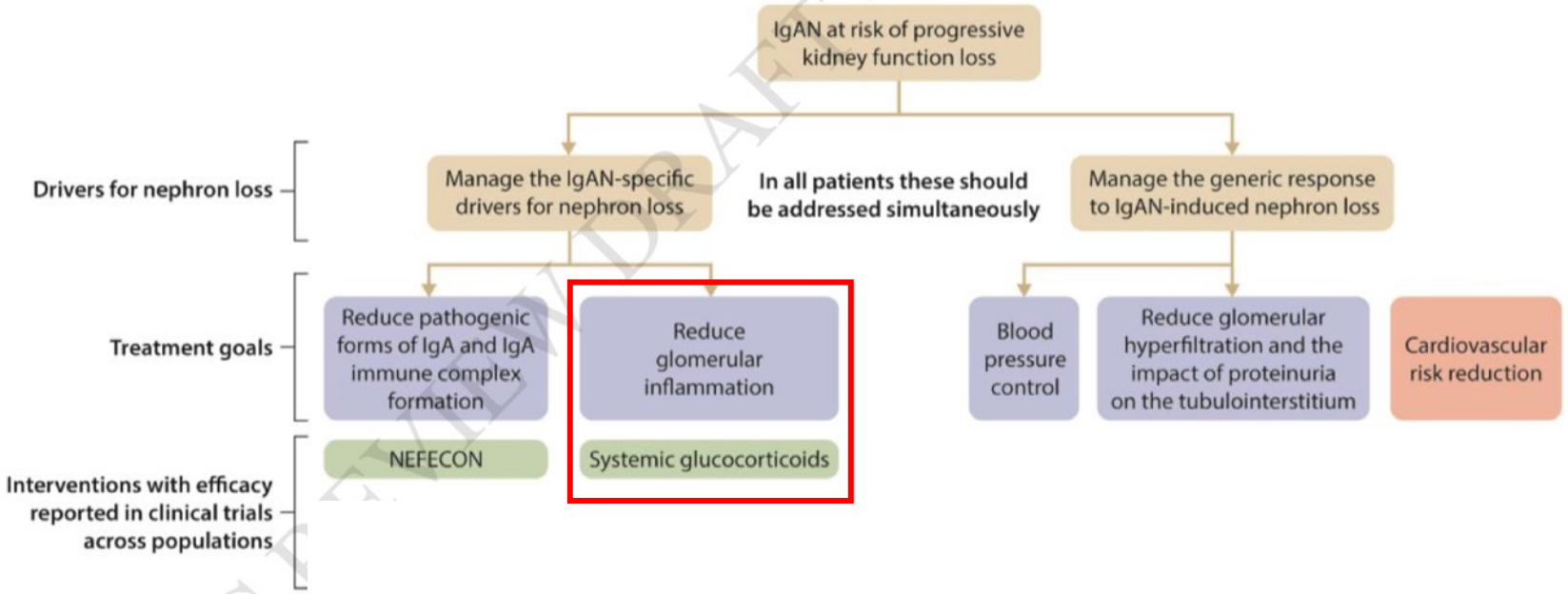
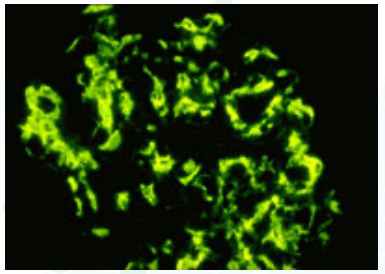
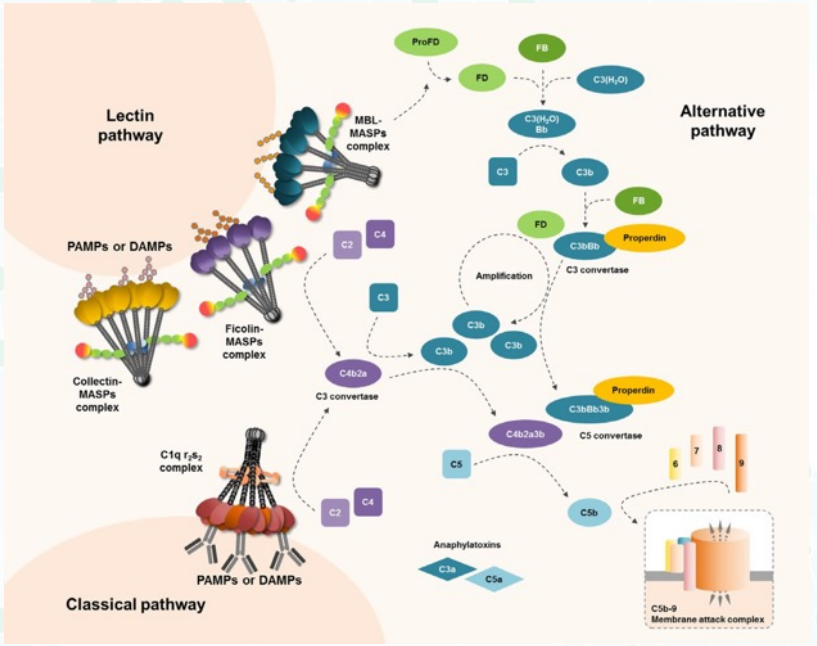


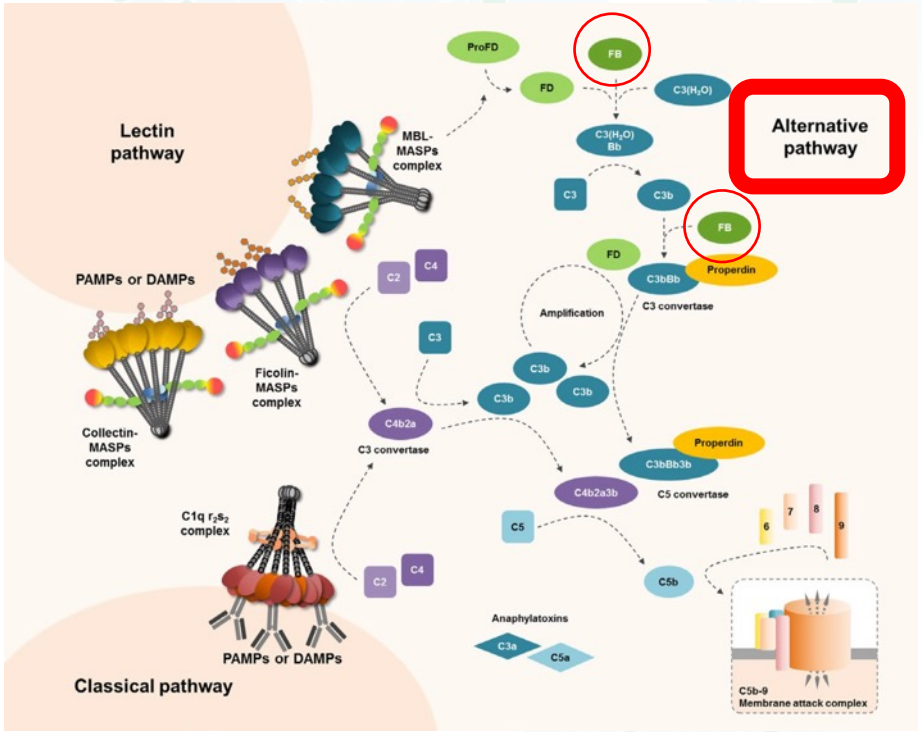
Figure 3 | Treatment targets in immunoglobulin A nephropathy (IgAN) and available to-date approved treatment options. *Measures to reduce glomerular hyperfiltration and the impact of proteinuria on the tubulointerstitium, using singly or in combination, renin-angiotensin system (RAS) blockade sparsentan, and sodium-glucose cotransporter-2 inhibition (SGLT2i). RASi, renin-angiotensin system inhibitors.



Inflammation



Complement inhibitors



ACTIVE, NOT RECRUITING

Study of Efficacy and Safety of LNP023 in Primary IgA Nephropathy Patients (APPLAUSE-IgAN)

ClinicalTrials.gov ID NCT04578834

Sponsor Novartis Pharmaceuticals

Information provided by Novartis (Novartis Pharmaceuticals) (Responsible Party)

Last Update Posted 2024-05-03

RECRUITING

A Study to Evaluate the Efficacy and Safety of RO7434656 in Participants With Primary Immunoglobulin A (IgA) Nephropathy at High Risk of Progression (IMAGINATION)

ClinicalTrials.gov ID NCT05797610

Sponsor Hoffmann-La Roche

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Last Update Posted 2024-05-10

RECRUITING

Study of ARO-CFB in Adult Healthy Volunteers and Patients With Complement-Mediated Kidney Disease

ClinicalTrials.gov ID NCT06209177

Sponsor Arrowhead Pharmaceuticals

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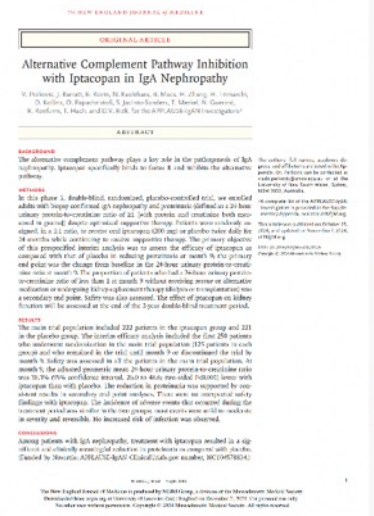
Last Update Posted 2024-04-24



ORIGINAL ARTICLE

Alternative Complement Pathway Inhibition with Iptacopan in IgA Nephropathy

www.kidney-international.org clinical trial

Results of a randomized double-blind placebo-controlled Phase 2 study propose iptacopan as an alternative complement pathway inhibitor for IgA nephropathy

see commentary on page 28

OPEN

Hong Zhang[1], Dana V. Rizk[2], Vlado Perkovic[3], Bart Maes[4], Naoki Kashihara[5], Brad Rovin[6], Heman Trimarchi[7], Ben Sprangers[8,9], Matthias Meier[10], Dmitrij Kollins[10], Olympia Papachristofi[10], Julie Milojevic[11], Guido Junge[11], Prasanna Kumar Nidamarthy[12], Alan Charney[13] and Jonathan Barratt[14,15]

Targeting the alternative complement pathway is an attractive therapeutic strategy given its role in the pathogenesis of immunoglobulin A nephropathy (IgAN). Iptacopan (LNP023) is an oral, proximal alternative complement inhibitor that specifically binds to Factor B. Our randomized, double-blind, parallel-group adaptive Phase 2 study (NCT03373461) enrolled patients with biopsy-confirmed IgAN (within previous three years) with estimated glomerular filtration rates of 30 mL/min/1.73 m² and over and urine protein 0.75 g/24 hours and over on stable doses of renin angiotensin system inhibitors. Patients were randomized to four iptacopan doses (10, 50, 100, or 200 mg bid) or placebo for either a three-month (Part 1; 46 patients) or a six-month (Part 2; 66 patients) treatment period. The primary analysis evaluated the dose-response relationship of iptacopan versus placebo on 24-hour urine protein-to-creatinine ratio (UPCR) at three months. Other efficacy, safety and biomarker parameters were assessed. Baseline characteristics were generally well-balanced across treatment arms. There was a statistically significant dose-response effect, with 23% reduction in UPCR achieved with iptacopan 200 mg bid (80% confidence interval 8-34%) at three months. UPCR decreased further through six months in iptacopan 100 and 200 mg arms (from a mean of 1.3 g/g at baseline to 0.8 g/g at six months in the 200 mg arm). A sustained reduction in complement biomarker levels including plasma Bb, serum Wieslab, and urinary C5b-9 was observed. Iptacopan was well-tolerated, with no reports of deaths, treatment-related serious adverse events or bacterial infections, and led to strong inhibition of alternative complement pathway activity and persistent proteinuria reduction in patients with IgAN. Thus, our findings support further evaluation of iptacopan in the ongoing Phase 3 trial (APPLAUSE-IgAN; NCT04578834).

Kidney International (2024) **105**, 189–199; https://doi.org/10.1016/j.kint.2023.09.027

KEYWORDS: alternative pathway biomarkers; complement; IgA nephropathy; iptacopan (LNP023) proteinuria

IgA nephropathy (IgAN) is the most common form of glomerulonephritis,[1] with a global incidence of approximately 25 per million per year.[2] There are regional variations in biopsy practices and in the occurrence of IgAN, with a higher prevalence rate and a higher risk of progression to kidney failure observed in Asians.[3,4] Around 15% to 40% of patients with IgAN may develop kidney failure within 10 to 20 years of diagnosis, placing considerable socioeconomic burden on individuals, caregivers, and health care systems globally.[5,6] Risk factors for progression to kidney failure include persistent high proteinuria (>1 g/d), hypertension, reduced glomerular filtration rate (GFR), and histologic MEST-C score at diagnosis.[7–10]

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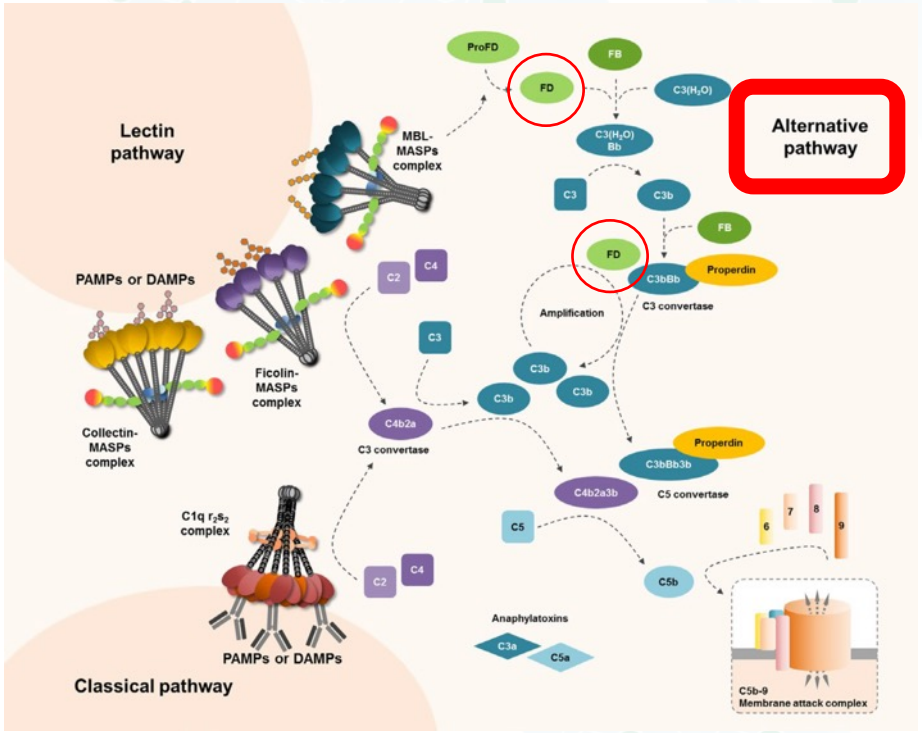


RECRUITING

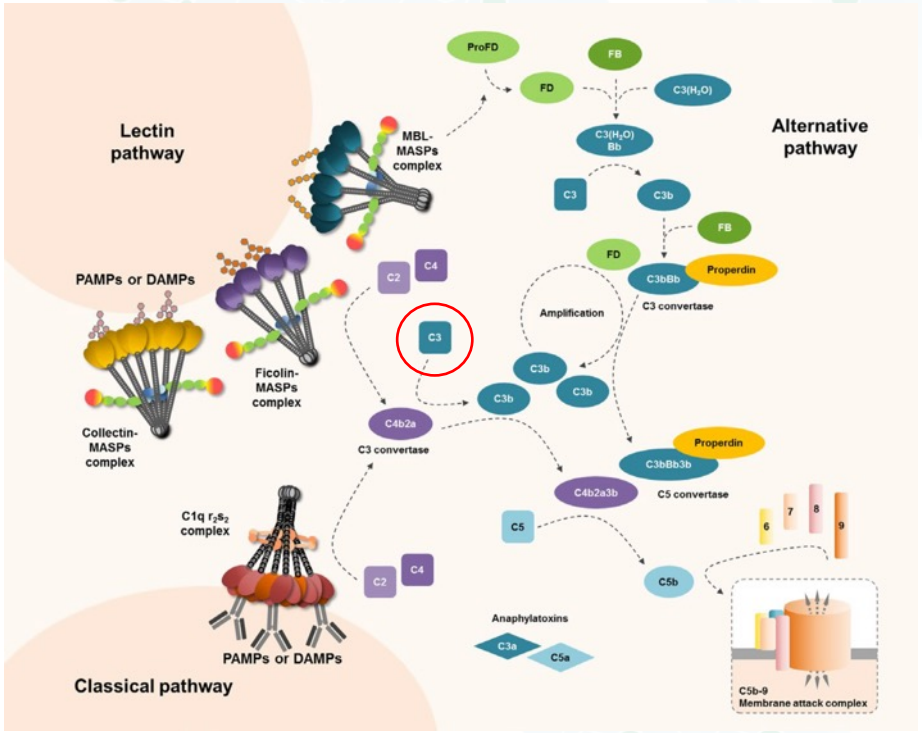
Study of ALXN2050 in Proliferative Lupus Nephritis (LN) or Immunoglobulin A Nephropathy (IgAN)

ClinicalTrials.gov ID NCT05097989

Sponsor Alexion Pharmaceuticals, Inc.

Information provided by Alexion Pharmaceuticals, Inc. (Responsible Party)

Last Update Posted 2024-04-11



KI REPORTS
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CLINICAL RESEARCH

Clinical Safety and Efficacy of Pegcetacoplan in a Phase 2 Study of Patients with C3 Glomerulopathy and Other Complement-Mediated Glomerular Diseases

Bradley P. Dixon[1], Larry A. Greenbaum[2], Liwei Huang[3], Sandeep Rajan[4], Chunlei Ke[5], Yiwei Zhang[5] and Li Li[5]

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Introduction: Dysregulated complement activation is likely the primary driver of disease in C3 glomerulopathy (C3G) and contributes to other complement-mediated diseases, including immunoglobulin A nephropathy (IgAN), lupus nephritis (LN), and primary membranous nephropathy (PMN). No complement inhibitors are proven to halt disease progression in these diseases. Pegcetacoplan, a targeted C3 and C3b inhibitor, may mitigate complement-mediated kidney damage in C3G and other glomerular diseases in which complement may have a pathogenic role.

Methods: This open-label, phase 2, 48-week study evaluated the preliminary efficacy and safety of subcutaneous pegcetacoplan for patients with complement-mediated glomerular diseases. The primary end point was proteinuria reduction, measured as 24-hour urine protein-to-creatinine ratio. Secondary end points included remission status, changes in estimated glomerular filtration rate (eGFR), and pharmacodynamic biomarkers. Treatment-emergent adverse events (TEAEs) were monitored.

Results: Efficacy results for the C3G cohort are reported herein, along with safety results for the study population. In the C3G cohort, mean proteinuria reduction from baseline to week 48 was 50.9% in the intent-to-treat (ITT) population ($n = 7$) and 65.4% in the per-protocol (PP) population ($n = 4$). Mean serum albumin normalized and mean eGFR was stable over 48 weeks. Mean serum C3 levels increased 6-fold and mean soluble C5b-9 levels decreased by 57.3% at week 48. The most common adverse events (AEs) were upper respiratory tract infection, injection site erythema, nausea, and headache. No meningitis or sepsis cases were reported, and no serious treatment-related AEs were observed.

Conclusion: Pegcetacoplan may provide therapeutic benefit for C3G and has a favorable safety profile across the 4 glomerular diseases studied.

Kidney Int Rep (2023) **8**, 2284–2293; https://doi.org/10.1016/j.ekir.2023.08.033

KEYWORDS: complement; C3 glomerulopathy; end-stage kidney disease; glomerulonephritis; pegcetacoplan; proteinuria

The complement system contributes to innate and acquired immunity through activation of the classical, lectin, and alternative pathways.[1,2] Activation of the complement pathways triggers a cascade, leading to inflammation, as well as opsonization and subsequent phagocytosis and cellular lysis, and ultimately elimination of an invading pathogen or damaged tissue.[1,4] These 3 activation pathways converge at C3, which plays a central role in the complement system and is key for activation of downstream terminal pathways, including formation of the membrane attack complex.[3,6]

Dysregulated activation of complement has been implicated in the pathogenesis of various forms of glomerulonephritis, including C3G, IgAN, LN, and PMN.[7,8] The etiology of complement dysregulation in

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RECRUITING

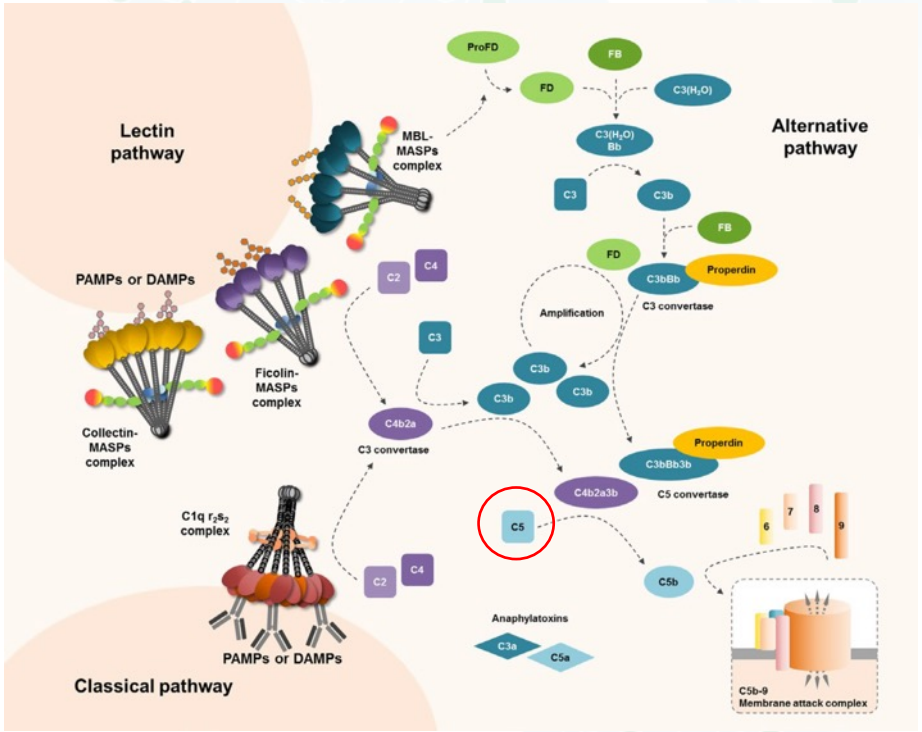
Study of ARO-C3 in Adult Healthy Volunteers and Patients With Complement Mediated Renal Disease

ClinicalTrials.gov ID NCT05083364

Sponsor Arrowhead Pharmaceuticals

Information provided by Arrowhead Pharmaceuticals (Responsible Party)

Last Update Posted 2024-04-15



Original Article

OPEN

Phase 2 Trial of Cemdisiran in Adult Patients with IgA Nephropathy: A Randomized Controlled Trial

Clinical Research

OPEN

Efficacy and Safety of Ravulizumab in IgA Nephropathy
A Phase 2 Randomized Double-Blind Placebo-Controlled Trial

RECRUITING

Study of Ravulizumab in Immunoglobulin A Nephropathy (IgAN) (ICAN)

ClinicalTrials.gov ID NCT06291376

Sponsor Alexion Pharmaceuticals, Inc.

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Last Update Posted 2024-05-03

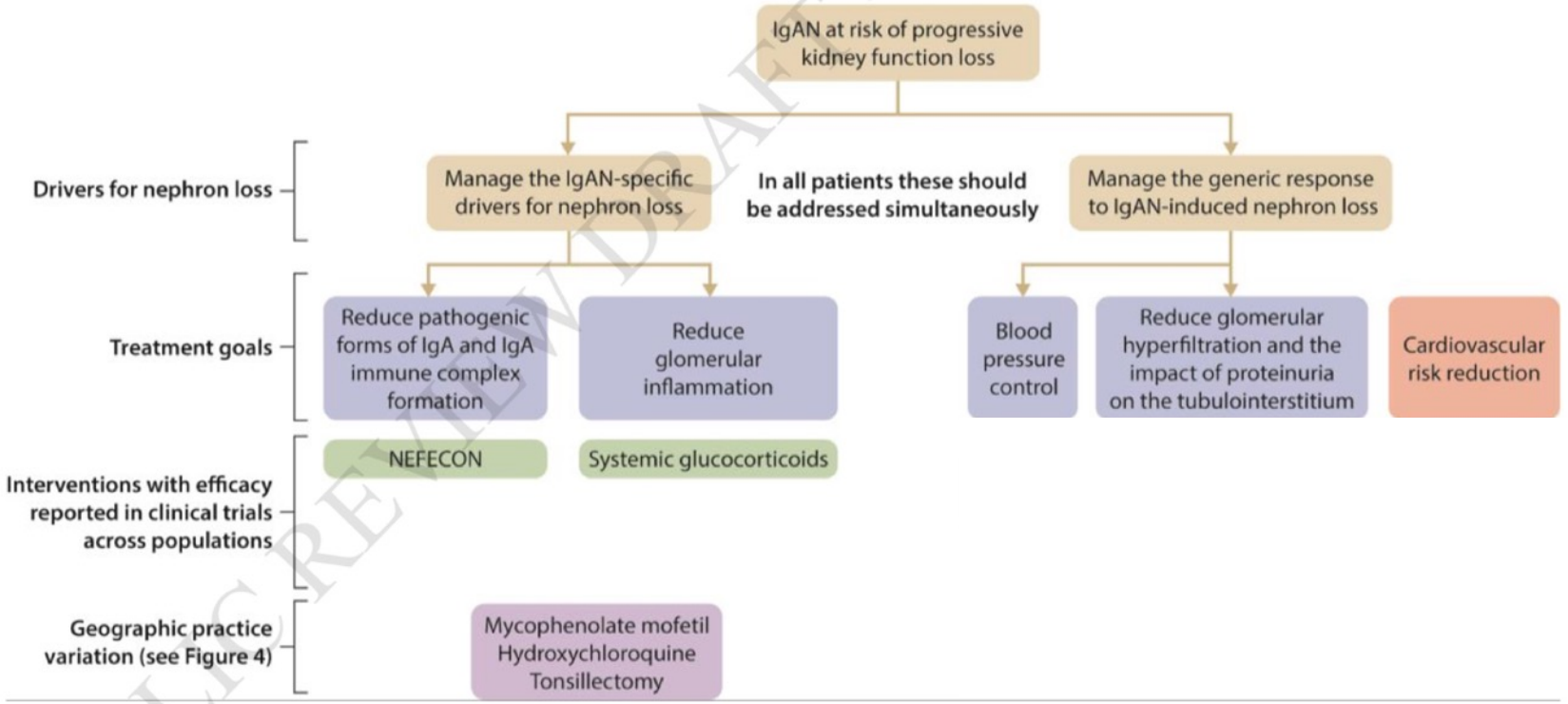


Figure 3 | Treatment targets in immunoglobulin A nephropathy (IgAN) and available to-date approved treatment options. *Measures to reduce glomerular hyperfiltration and the impact of proteinuria on the tubulointerstitium, using singly or in combination, renin-angiotensin system (RAS) blockade sparsentan, and sodium-glucose cotransporter-2 inhibition (SGLT2i). RASi, renin-angiotensin system inhibitors.

2.3.3 Managing the IgAN-specific drivers for nephron loss

2.3.3.1 Reducing the production of pathogenic forms of IgA and IgA immune complex formation

Recommendation 2.3.3.1.1: We suggest treatment with a 9-month course of nefecon for patients who are at risk of progressive kidney function loss with IgAN *(2B)*.

Practice Point 2.3.3.1.1: Factors to consider before using nefecon in patients with IgAN

- **A single 9-month treatment course of nefecon is unlikely to produce a sustained clinical response in terms of proteinuria reduction or stabilization of eGFR and it is likely that many patients will need either repeated 9-month treatment cycles or a reduced-dose maintenance regimen**
- **The approval status, labelled indication and availability vary globally.**

Practice Point 2.3.3.1.2: Other pharmacologic therapies evaluated in IgAN:

- **Multiple agents have been evaluated in often small studies, in restricted populations and have failed to show a consistent benefit in IgAN (Figure 4)**

Agent	Suggested usage	Remarks
Antiplatelet agents	Not recommended	No evidence of efficacy
Anticoagulants	Not recommended	No evidence of efficacy
Azathioprine	Not recommended	No evidence for efficacy as monotherapy or when combined wit glucocorticoids
Cyclophosphamide	Not recommended	Unless in the setting of rapidly progressive IgAN
Calcineurin inhibitors	Not recommended	No evidence of efficacy
Rituximab	Not recommended	No evidence of efficacy
Fish oil	Not recommended	Patients who wish to take fish oil should be advised of the dose and formulation used in the published clinical trials that reported efficacy.
Mycophenolate mofetil (MMF)	**Chinese patients** In those patients in whom glucocorticoids are being considered MMF may be used as a glucocorticoid-sparing agent	Three RCTs have been conducted in China: the first from Hong Kong (n=40, eGFR ~51 ml/min/1.73 m^2) showed a significant reduction in time-averaged proteinuria after MMF (1.5 to 2.0 g/day for 6 months) was added to SC in patients with proteinuria >1 g/d.[1] An extended 6-year follow-up showed a lesser slope of eGFR decline and lower probability of reaching kidney failure in MMF-treated patients;[2] the second from around Jiangsu (n=176, eGFR >90 ml/min/1.73 m^2) showed that MMF with low-dose glucocorticoids (0.4–0.6 mg/kg/d prednisone) for 6 months was non-inferior to standard-dose glucocorticoids (0.8–1.0 mg/kg/d) for the treatment of incident IgAN presenting with proliferative histologic lesions (E or C lesions with or without necrosis) on kidney biopsy and proteinuria >1.0 g/d.[3] There were significantly fewer glucocorticoid-related side-effects in the combination-therapy arm; the third from Guangdong (n=170, eGFR 50 ml/min/1.73 m^2) showed that MMF (initially, 1.5 g/d for 12 months, maintained at 0.75–1.0 g/d for at least 6 months) and SC reduced the frequency of the primary composite outcome (doubling of serum creatinine, kidney failure, or death due to kidney or cardiovascular causes, aHR 0.23; 95% CI, 0.09–0.63) and CKD progression (aHR 0.23; 95% CI, 0.1–0.57) compared to SC alone.[4] MMF was well tolerated in all the 3 trials.
	Non-Chinese patients There is insufficient evidence to support the use of MMF	In three smaller RCTs of MMF in non-Chinese patients there was no evidence for efficacy of MMF monotherapy: these were from Belgium (n=34, inulin clearance ~71 ml/min/1.73 m^2),[5] New York (n=32, eGFR ~39 ml/min/1.73 m^2 and required glomerulosclerosis or tubulointerstitial atrophy and fibrosis on kidney biopsy reflecting relatively advanced CKD already)[6] and US/Canada (n=44, eGFR >90 ml/min/1.73 m^2, MMF versus omega-3 fatty acid).[7]
Hydroxychloroquine	**Chinese patients** In those patients who remain at high risk of progression in spite of optimized supportive care	In a small, short-term RCT conducted in China, hydroxychloroquine introduced to patients with proteinuria of 0.75–3.5 g/d despite optimized ACEi/ARB reduced proteinuria by 48% versus 10% in the placebo group at 6 months.[8]
	Non-Chinese patients There is insufficient evidence to support the use in those patients	Hydroxychloroquine has not been evaluated in non-Chinese patients.

Figure 4 | Other pharmacologic therapies evaluated in immunoglobulin A nephropathy (IgAN). [1]Tang *et al.*[28], [2]Tang *et al.*[29], [3]Hou *et al.*[30], [4]Hou *et al.*[31], [5]Maes *et al.*,[32] [6]Frisch *et al.*,[33] [7]Hogg *et al.*,[34] [8]Liu *et al.*[35], ACEi, angiotensin-converting enzyme inhibitor; aHR, adjusted hazard ratio; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; CI, confidence interval; IgAN, immunoglobulin A nephropathy; KRT, kidney replacement therapy; MMF, mycophenolate mofetil; RCT, randomized controlled trial; SC, standard of care; SCr, serum creatinine.

JAMA Network | Open.

Original Investigation | Nephrology

Effectiveness of Mycophenolate Mofetil Among Patients With Progressive IgA Nephropathy
A Randomized Clinical Trial

Fan Fan Hou, MD, PhD; Di Xie, MD, PhD; Jun Wang, MD, PhD; Xin Xu, MD, PhD; Xiaobing Yang, MD, PhD; Jun Ai, MD, PhD; Sheng Nie, MD, PhD; Min Liang, MD, PhD; Guobao Wang, MD; Nan Jia, MD, PhD; for the MAIN Trial Investigators

Abstract

IMPORTANCE The role of mycophenolate mofetil (MMF) in management of immunoglobulin A nephropathy (IgAN) remains highly controversial.

OBJECTIVE To evaluate the efficacy and safety of MMF in patients with IgAN at high risk of kidney function loss.

DESIGN, SETTING, AND PARTICIPANTS This randomized clinical trial with open-label, blinded end-point design was conducted among adults with IgAN, proteinuria greater than 1.0 g/d, and estimated glomerular filtration rate (eGFR) greater than 30 and less than 60 mL/min/1.73m^2 or with persistent hypertension from September 2013 to December 2015. During a 3-month run-in period, 238 patients received optimized supportive care (SC), including losartan. Patients with a urinary protein excretion rate of 0.75 g/d or greater despite of 3 months optimized SC were enrolled into the trial for 3 years. Survivors of the trial who did not receive dialysis or transplant were followed up after the trial for a median (IQR) of 60 (47-76) months. Data were analyzed from March through June 2022.

INTERVENTIONS A total of 170 participants were randomized in a 1:1 ratio to receive MMF (initially, 1.5 g/d for 12 months, maintained at 0.75-1.0 g for at least 6 months) plus SC or SC alone.

MAIN OUTCOMES AND MEASURES The primary outcomes were (1) a composite of doubling of serum creatinine, end-stage kidney disease (dialysis, transplant, or kidney failure without receiving kidney replacement therapy), or death due to kidney or cardiovascular cause and (2) progression of chronic kidney disease.

RESULTS Among 170 randomized patients (mean [SD] age 36.6 [9.4] years; 94 [55.3%] male patients), 85 patients received MMF with SC and 85 patients received SC alone. The mean (SD) eGFR was 50.1 (17.9) mL/min/1.73m^2 and mean (SD) proteinuria level was 1.9 (1.7) g/d; 168 patients (98.8%) completed the trial, and 157 participants (92.4%) survived and did not receive dialysis or transplant. Primary composite outcome events occurred in 6 patients (7.1%) in the MMF group and 18 patients (21.2%) in the SC group (adjusted hazard ratio [aHR], 0.23; 95% CI, 0.09-0.63). Progression of chronic kidney disease occurred in 7 participants (8.2%) in the MMF group and 23 participants (27.1%) in the SC group (aHR, 0.23; 95% CI, 0.10-0.57). The effect of MMF treatment on primary outcomes was consistent across prespecified subgroups, with no significant interaction per subgroup. During posttrial follow-up, annual loss of eGFR accelerated after discontinuation of MMF; mean (SD) annual eGFR loss during the study period was 2.9 (1.0) mL/min/1.73m^2 in the MMF group

(continued)

Key Points

Question Is mycophenolate mofetil (MMF) effective in patients with immunoglobulin A (IgA) nephropathy at high risk of kidney function loss treated with optimized supportive care?

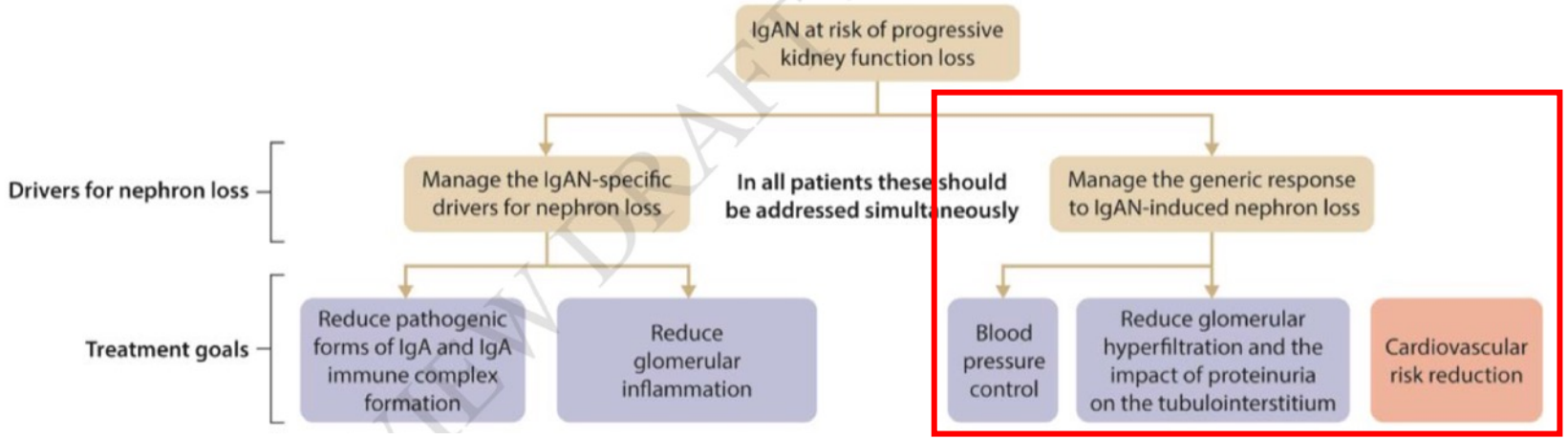
Findings In this randomized clinical trial including 170 participants with IgA nephropathy, the addition of MMF to optimized supportive care significantly reduced risk of a composite outcome (creatinine doubling, indication for kidney replacement therapy, or death due to kidney or cardiovascular cause) and progression of chronic kidney disease.

Meaning These findings suggest that MMF may be beneficial in patients with progressive IgA nephropathy.

+ Visual Abstract
+ Supplemental content

Author affiliations and article information are listed at the end of this article.

JAMA Network Open. 2023;6(2):e2254054. doi:10.1001/jamanetworkopen.2022.54054 February 6, 2023 1/14



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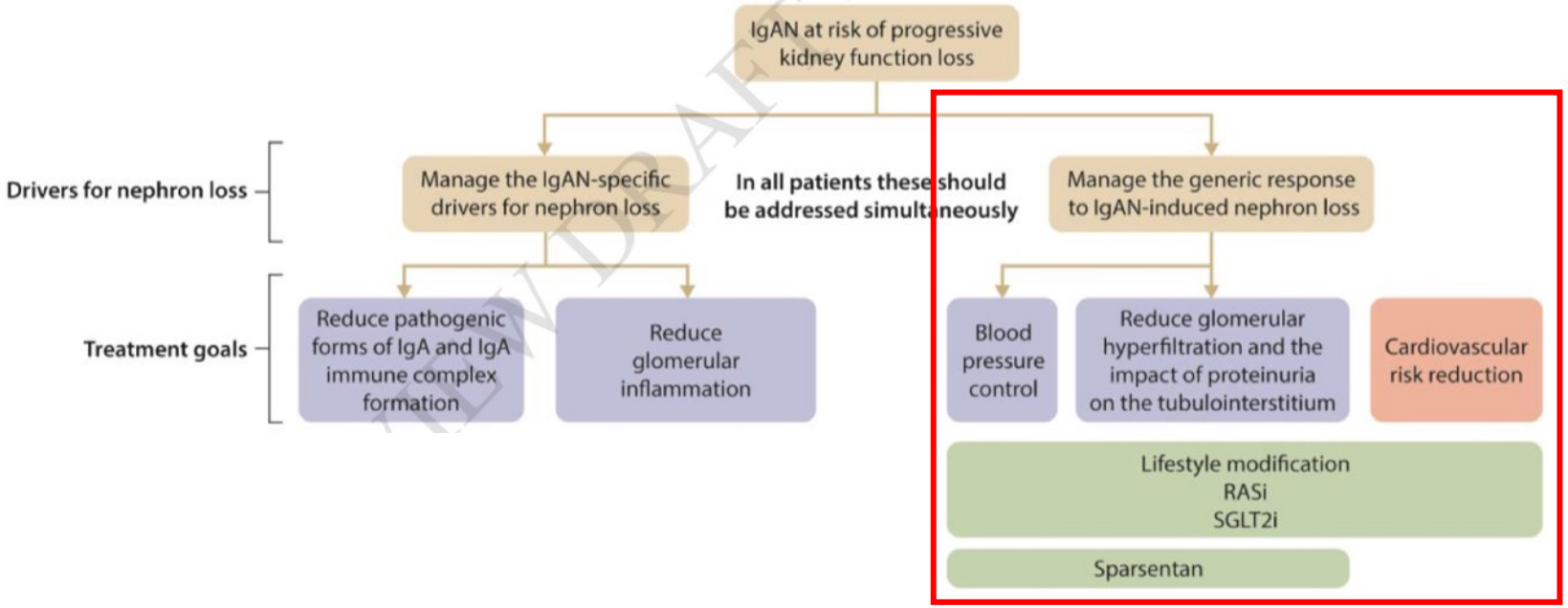

Figure 3 | Treatment targets in immunoglobulin A nephropathy (IgAN) and available to-date approved treatment options. *Measures to reduce glomerular hyperfiltration and the impact of proteinuria on the tubulointerstitium, using singly or in combination, renin-angiotensin system (RAS) blockade sparsentan, and sodium-glucose cotransporter-2 inhibition (SGLT2i). RASi, renin-angiotensin system inhibitors.

2.3.4 Managing the responses to IgAN-induced nephron loss

Practice Point 2.3.4.1: Interventions for all patients with IgAN:

- **Control blood pressure to a target of ≤120/70 mm Hg, using a RASi as the first choice drug intervention**
- **Lifestyle advice should be given, where appropriate, on smoking cessation, weight reduction, dietary sodium restriction (<2 g/d) and regular exercise.**
- **A cardiovascular risk assessment should be undertaken and interventions commenced as per local guidelines.**

Recommendation 2.3.4.1: We recommend all patients who are at risk of progressive kidney function loss with IgAN be treated with an optimized maximally tolerated dose of either an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) *(1B)*.

Recommendation 2.3.4.2: We suggest that patients who are at risk of progressive kidney function loss with IgAN be treated with a sodium-glucose cotransporter-2 inhibitor (SGLT2i) *(2B)*.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators*

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Heerspink at the Department of Clinical Pharmacy and Pharmacology, University of Groningen, P.O. Box 30.001, 9700 RB Groningen, the Netherlands, or at h.j.lambers.heerspink@umcg.nl.

*A complete list of DAPA-CKD committee members and investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 24, 2020, at NEJM.org.

N Engl J Med 2020;383:1436-46.
DOI: 10.1056/NEJMoa2024816

ABSTRACT

BACKGROUND

Patients with chronic kidney disease have a high risk of adverse kidney and cardiovascular outcomes. The effect of dapagliflozin in patients with chronic kidney disease, with or without type 2 diabetes, is not known.

METHODS

We randomly assigned 4304 participants with an estimated glomerular filtration rate (GFR) of 25 to 75 ml per minute per 1.73 m^2 of body-surface area and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 200 to 5000 to receive dapagliflozin (10 mg once daily) or placebo. The primary outcome was a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes.

RESULTS

The independent data monitoring committee recommended stopping the trial because of efficacy. Over a median of 2.4 years, a primary outcome event occurred in 197 of 2152 participants (9.2%) in the dapagliflozin group and 312 of 2152 participants (14.5%) in the placebo group (hazard ratio, 0.61; 95% confidence interval [CI], 0.51 to 0.72; P<0.001; number needed to treat to prevent one primary outcome event, 19 [95% CI, 15 to 27]). The hazard ratio for the composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes was 0.56 (95% CI, 0.45 to 0.68; P<0.001), and the hazard ratio for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71 (95% CI, 0.55 to 0.92; P=0.009). Death occurred in 101 participants (4.7%) in the dapagliflozin group and 146 participants (6.8%) in the placebo group (hazard ratio, 0.69; 95% CI, 0.53 to 0.88; P=0.004). The effects of dapagliflozin were similar in participants with type 2 diabetes and in those without type 2 diabetes. The known safety profile of dapagliflozin was confirmed.

CONCLUSIONS

Among patients with chronic kidney disease, regardless of the presence or absence of diabetes, the risk of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo. (Funded by AstraZeneca; DAPA-CKD ClinicalTrials.gov number, NCT03036150.)

A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy

see commentary on page 24
OPEN

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Immunoglobulin A (IgA) nephropathy is a common form of glomerulonephritis, which despite use of renin-angiotensin-aldosterone-system blockers and immunosuppressants, often progresses to kidney failure. In the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease trial, dapagliflozin reduced the risk of kidney failure and prolonged survival in participants with chronic kidney disease with and without type 2 diabetes, including those with IgA nephropathy. Participants with estimated glomerular filtration rate (eGFR) 25-75 mL/min/1.73m² and urinary albumin-to-creatinine ratio 200-5000 mg/g (22.6-565 mg/mol) were randomized to dapagliflozin 10mg or placebo, as adjunct to standard care. The primary composite endpoint was a sustained decline in eGFR of 50% or more, end-stage kidney disease, or death from a kidney disease-related or cardiovascular cause. Of 270 participants with IgA nephropathy (254 [94%] confirmed by previous biopsy), 137 were randomized to dapagliflozin and 133 to placebo, and followed for median 2.1 years. Overall, mean age was 51.2 years; mean eGFR, 43.8 mL/min/1.73m²; and median urinary albumin-to-creatinine ratio, 900 mg/g. The primary outcome occurred in six (4%) participants on dapagliflozin and 20 (15%) on placebo (hazard ratio, 0.29; 95% confidence interval, 0.12, 0.73). Mean rates of eGFR decline with dapagliflozin and placebo were −3.5 and −4.7 mL/min/1.73m²/year, respectively. Dapagliflozin reduced the urinary albumin-to-creatinine ratio by 26% relative to placebo. Adverse events leading to study drug discontinuation were similar with dapagliflozin and placebo. There were fewer serious adverse events with dapagliflozin, and no new safety findings in this population. Thus, in participants with IgA nephropathy, dapagliflozin reduced the risk of chronic kidney disease progression with a favorable safety profile.

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KEYWORDS: chronic kidney disease; dapagliflozin; DAPA-CKD; IgA nephropathy; randomized controlled clinical trial; sodium-glucose cotransporter inhibitor

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IgA nephropathy is the most common primary glomerular disease worldwide.[1] Despite advances in our understanding of its pathogenesis, treatment strategies have changed little over the last 2 or 3 decades.[2] Over a period of 4 to 15 years (mean, 6.1 years), approximately 30% of patients with IgA nephropathy progress to kidney failure, and risk factors for

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RESEARCH SUMMARY

Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group DOI: 10.1056/NEJMoa2204233

CLINICAL PROBLEM

Sodium–glucose cotransporter 2 inhibitors appear to slow the progression of kidney disease in patients with diabetes and albuminuria. However, most patients with chronic kidney disease do not have diabetes and have low levels of albuminuria, and the effects of empagliflozin therapy in these patients are unclear.

CLINICAL TRIAL

Design: This international, randomized, parallel-group, double-blind, placebo-controlled trial assessed the efficacy of empagliflozin in patients with chronic kidney disease, with or without diabetes and with a range of albuminuria levels.

Intervention: 6609 patients with an estimated glomerular filtration rate (eGFR) of 20 to <45 ml per minute per 1.73 m^2 of body-surface area, or with an eGFR of 45 to <90 ml per minute per 1.73 m^2 and a urinary albumin-to-creatinine ratio of ≥200 (with albumin measured in milligrams and creatinine measured in grams), were assigned to receive 10 mg of empagliflozin or placebo daily. In this study, 54% of patients had chronic kidney disease without diabetes and 34% had an eGFR of <30 ml per minute per 1.73 m^2. The primary outcome was the first occurrence of progression of kidney disease or death from cardiovascular causes.

RESULTS

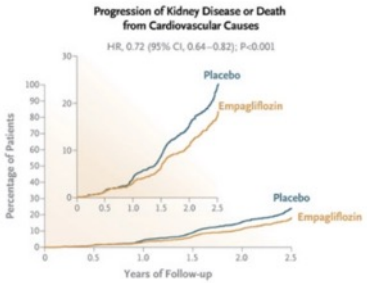
Efficacy: During a median follow-up of 2 years, progression of kidney disease or death from cardiovascular causes occurred in a significantly smaller percentage of patients in the empagliflozin group than in the placebo group.

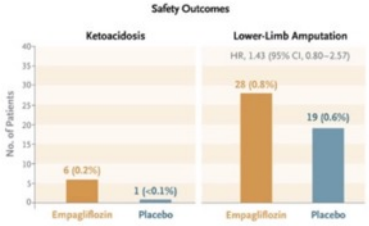
Safety: Ketoacidosis occurred in numerically more patients in the empagliflozin group than in the placebo group, as did lower-limb amputations. The incidence of serious adverse events overall and according to major organ class was similar in the two groups.

LIMITATIONS AND REMAINING QUESTIONS

- Fewer cardiovascular events occurred than expected, potentially affecting secondary and tertiary outcome assessments.
- Further study of patients with a urinary albumin-to-creatinine ratio of less than 300 may be useful.

Links: Full Article | NEJM Quick Take | Editorial





CONCLUSIONS

Among a wide range of patients with chronic kidney disease who were at risk for progression, empagliflozin therapy was associated with a lower risk of disease progression or death from cardiovascular causes than placebo.

Recommendation 2.3.4.2: We suggest that patients who are at risk of progressive kidney function loss with IgAN be treated with a sodium-glucose cotransporter-2 inhibitor (SGLT2i) *(2B)*.

Practice Point 2.3.4.2: Factors to consider before using an SGLT2i in patients with IgAN:

- **There was no requirement for patients with IgAN to be on an optimized maximally tolerated dose of RASi for a minimum of 3 months for inclusion in The Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY) and Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trials.**
- **IgAN patients included in EMPA-KIDNEY and DAPA-CKD likely had longstanding disease, based on the age and eGFR at randomization; therefore, there is uncertainty over the value of SGLT2i in patients with IgAN and a relatively preserved eGFR (>60 ml/min per 1.73 m^2) (see Table 2).**

Recommendation 2.3.4.3: We suggest that patients who are at risk of progressive kidney function loss with IgAN be treated with sparsentan *(2B)*.

Sparsentan in patients with IgA nephropathy: a prespecified interim analysis from a randomised, double-blind, active-controlled clinical trial

Hiddo J L Heerspink, Jai Radhakrishnan, Charles E Alpers, Jonathan Barratt, Stewart Bieler, Ulysses Diva, Jula Inrig, Radko Komers, Alex Mercer, Irene L Noronha, Michelle N Rheault, William Rote, Brad Rovin, Howard Trachtman, Hernán Trimarchi, Muh Geot Wong, Vlado Perkovic, for the PROTECT Investigators*

Summary

Background Sparsentan is a novel, non-immunosuppressive, single-molecule, dual endothelin and angiotensin receptor antagonist being examined in an ongoing phase 3 trial in adults with IgA nephropathy. We report the prespecified interim analysis of the primary proteinuria efficacy endpoint, and safety.

Methods PROTECT is an international, randomised, double-blind, active-controlled study, being conducted in 134 clinical practice sites in 18 countries. The study examines sparsentan versus irbesartan in adults (aged ≥18 years) with biopsy-proven IgA nephropathy and proteinuria of 1·0 g/day or higher despite maximised renin-angiotensin system inhibitor treatment for at least 12 weeks. Participants were randomly assigned in a 1:1 ratio to receive sparsentan 400 mg once daily or irbesartan 300 mg once daily, stratified by estimated glomerular filtration rate at screening (30 to <60 mL/min per 1·73 m² and ≥60 mL/min per 1·73 m²) and urine protein excretion at screening (≤1·75 g/day and >1·75 g/day). The primary efficacy endpoint was change from baseline to week 36 in urine protein–creatinine ratio based on a 24-h urine sample, assessed using mixed model repeated measures. Treatment-emergent adverse events (TEAEs) were safety endpoints. All endpoints were examined in all participants who received at least one dose of randomised treatment. The study is ongoing and is registered with ClinicalTrials.gov, NCT03762850.

Findings Between Dec 20, 2018, and May 26, 2021, 404 participants were randomly assigned to sparsentan (n=202) or irbesartan (n=202) and received treatment. At week 36, the geometric least squares mean percent change from baseline in urine protein–creatinine ratio was statistically significantly greater in the sparsentan group (–49·8%) than the irbesartan group (–15·1%), resulting in a between-group relative reduction of 41% (least squares mean ratio=0·59; 95% CI 0·51–0·69; p<0·0001). TEAEs with sparsentan were similar to irbesartan. There were no cases of severe oedema, heart failure, hepatotoxicity, or oedema-related discontinuations. Bodyweight changes from baseline were not different between the sparsentan and irbesartan groups.

Interpretation Once-daily treatment with sparsentan produced meaningful reduction in proteinuria compared with irbesartan in adults with IgA nephropathy. Safety of sparsentan was similar to irbesartan. Future analyses after completion of the 2-year double-blind period will show whether these beneficial effects translate into a long-term nephroprotective potential of sparsentan.

Funding Travere Therapeutics.

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*PROTECT Investigators are listed in the appendix (pp 2–5)

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Introduction

Immunoglobulin A (IgA) nephropathy is the most common primary glomerulonephritis and an important cause of kidney failure.[1,2] Proteinuria has been consistently shown to be a risk factor for progressive kidney function loss in patients with IgA nephropathy,[3] and remission of proteinuria is associated with improved kidney outcomes.[3] Despite the risk of progressive kidney disease and kidney failure, few therapeutic options are available. The Kidney Disease Improving Global Outcomes (KDIGO) guideline recommends the use of renin-angiotensin system (RAS) inhibitors in patients with proteinuria more than 0·5 g/day.[4] Following 3 months of RAS inhibitor treatment, patients with proteinuria of 1 g/day or higher have a greater risk of disease progression, and additional treatment is recommended.

The use of RAS inhibitors as standard of care in IgA nephropathy is based on their well established pleiotropic nephroprotective actions in a variety of kidney diseases and indicates a contribution of its main effector, angiotensin II, in the pathophysiology of IgA nephropathy.[5] More recently, advances in our understanding of the pathogenesis of IgA nephropathy show that endothelin-1 (ET-1) contributes to the pathophysiology of IgA nephropathy via activation of ET_A receptors, leading to a variety of effects including vasoconstriction, podocyte dysfunction, tubular injury, inflammation, and fibrosis.[6]

Efficacy and safety of sparsentan versus irbesartan in patients with IgA nephropathy (PROTECT): 2-year results from a randomised, active-controlled, phase 3 trial

Brad H Rovin*, Jonathan Barratt*, Hiddo J L Heerspink, Charles E Alpers, Stewart Bieler, Dong-Wan Chae, Ulysses A Diva, Jürgen Floege, Loreto Gesualdo, Jula K Inrig, Donald F Kohan, Radko Komers, Laura Ann Kooienga, Richard J Lafayette, Bart Maes, Robert Malecki, Alex Mercer, Irene L Noronha, Se Won Oh, Chen Au Peh, Manuel Praga, Priscila Preciado, Jai Radhakrishnan, Michelle N Rheault, William F Rote, Sydney C W Tang, Vladimir Tesar, Howard Trachtman, Hernán Trimarchi, James A Tumlin, Muh Geot Wong, Vlado Perkovic, on behalf of the DUPRO steering committee and PROTECT Investigators†

Summary

Background Sparsentan, a novel, non-immunosuppressive, single-molecule, dual endothelin angiotensin receptor antagonist, significantly reduced proteinuria versus irbesartan, an angiotensin II receptor blocker, at 36 weeks (primary endpoint) in patients with immunoglobulin A nephropathy in the phase 3 PROTECT trial's previously reported interim analysis. Here, we report kidney function and outcomes over 110 weeks from the double-blind final analysis.

Methods PROTECT, a double-blind, randomised, active-controlled, phase 3 study, was done across 134 clinical practice sites in 18 countries throughout the Americas, Asia, and Europe. Patients aged 18 years or older with biopsy-proven primary IgA nephropathy and proteinuria of at least 1·0 g per day despite maximised renin–angiotensin system inhibition for at least 12 weeks were randomly assigned (1:1) to receive sparsentan (target dose 400 mg oral sparsentan once daily) or irbesartan (target dose 300 mg oral irbesartan once daily) based on a permuted-block randomisation method. The primary endpoint was proteinuria change between treatment groups at 36 weeks. Secondary endpoints included rate of change (slope) of the estimated glomerular filtration rate (eGFR), changes in proteinuria, a composite of kidney failure (confirmed 40% eGFR reduction, end-stage kidney disease, or all-cause mortality), and safety and tolerability up to 110 weeks from randomisation. Secondary efficacy outcomes were assessed in the full analysis set and safety was assessed in the safety set, both of which were defined as all patients who were randomly assigned and received at least one dose of randomly assigned study drug. This trial is registered with ClinicalTrials.gov, NCT03762850.

Findings Between Dec 20, 2018, and May 26, 2021, 203 patients were randomly assigned to the sparsentan group and 203 to the irbesartan group. One patient from each group did not receive the study drug and was excluded from the efficacy and safety analyses (282 [70%] of 404 included patients were male and 272 [67%] were White) . Patients in the sparsentan group had a slower rate of eGFR decline than those in the irbesartan group. eGFR chronic 2-year slope (weeks 6–110) was −2·7 mL/min per 1·73 m² per year versus −3·8 mL/min per 1·73 m² per year (difference 1·1 mL/min per 1·73 m² per year, 95% CI 0·1 to 2·1; p=0·037); total 2-year slope (day 1–week 110) was −2·9 mL/min per 1·73 m² per year versus −3·9 mL/min per 1·73 m² per year (difference 1·0 mL/min per 1·73 m² per year, 95% CI −0·03 to 1·94; p=0·058). The significant reduction in proteinuria at 36 weeks with sparsentan was maintained throughout the study period; at 110 weeks, proteinuria, as determined by the change from baseline in urine protein-to-creatinine ratio, was 40% lower in the sparsentan group than in the irbesartan group (–42·8%, 95% CI –49·8 to –35·0, with sparsentan versus –4·4%, –15·8 to 8·7, with irbesartan; geometric least-squares mean ratio 0·60, 95% CI 0·50 to 0·72). The composite kidney failure endpoint was reached by 18 (9%) of 202 patients in the sparsentan group versus 26 (13%) of 202 patients in the irbesartan group (relative risk 0·7, 95% CI 0·4 to 1·2). Treatment-emergent adverse events were well balanced between sparsentan and irbesartan, with no new safety signals.

Interpretation Over 110 weeks, treatment with sparsentan versus maximally titrated irbesartan in patients with IgA nephropathy resulted in significant reductions in proteinuria and preservation of kidney function.

Funding Travere Therapeutics.

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Recommendation 2.3.4.3: We suggest that patients who are at risk of progressive kidney function loss with IgAN be treated with sparsentan *(2B)*.

Practice Point 2.3.4.3: Factors to consider before using sparsentan in patients with IgAN

- **Sparsentan is a dual endothelin angiotensin receptor antagonist (DEARA) and should not be prescribed together with a RASi.**
- **The approval status, labelled indication and availability vary globally.**

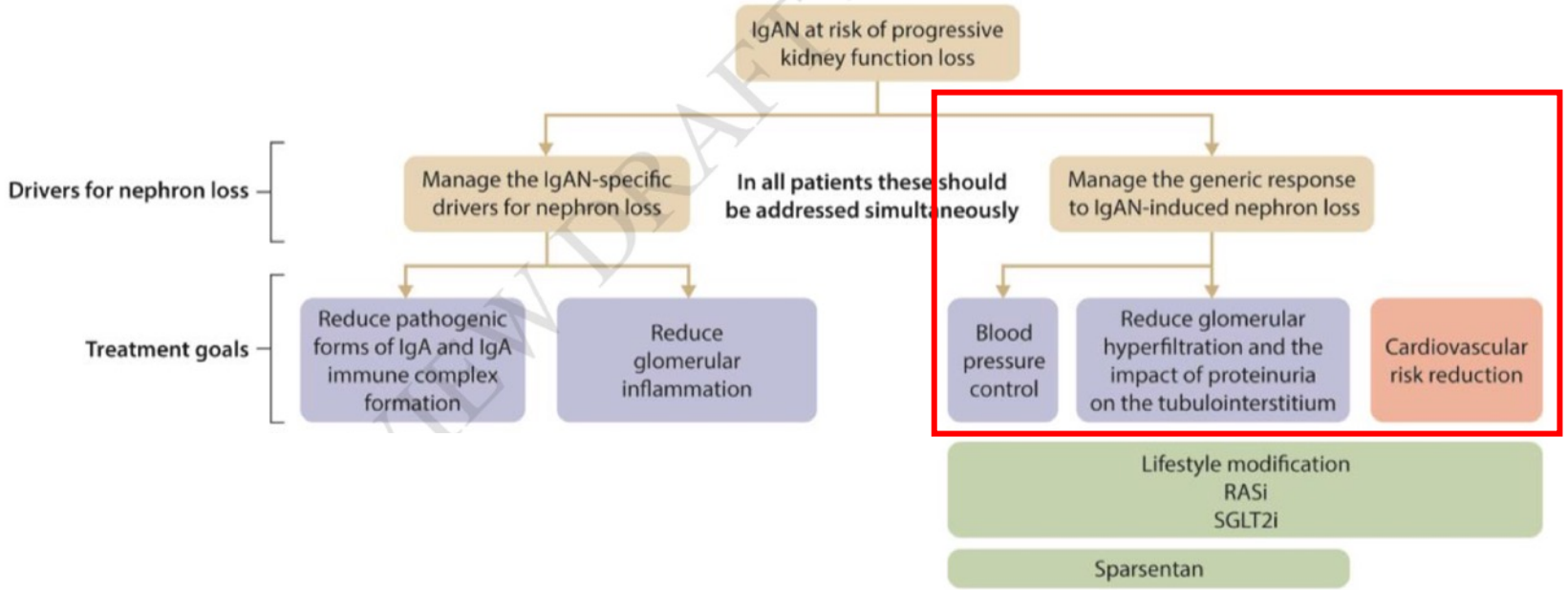

Figure 3 | Treatment targets in immunoglobulin A nephropathy (IgAN) and available to-date approved treatment options. *Measures to reduce glomerular hyperfiltration and the impact of proteinuria on the tubulointerstitium, using singly or in combination, renin-angiotensin system (RAS) blockade sparsentan, and sodium-glucose cotransporter-2 inhibition (SGLT2i). RASi, renin-angiotensin system inhibitors.

ACTIVE, NOT RECRUITING

Atrasentan in Patients With IgA Nephropathy (ALIGN)

ClinicalTrials.gov ID NCT04573478

Sponsor Chinook Therapeutics U.S., Inc.

Information provided by Chinook Therapeutics, Inc. (Chinook Therapeutics U.S., Inc.) (Responsible Party)

Last Update Posted 2024-05-03

ACTIVE, NOT RECRUITING

Atrasentan in Patients With Proteinuric Glomerular Diseases (AFFINITY)

ClinicalTrials.gov ID NCT04573920

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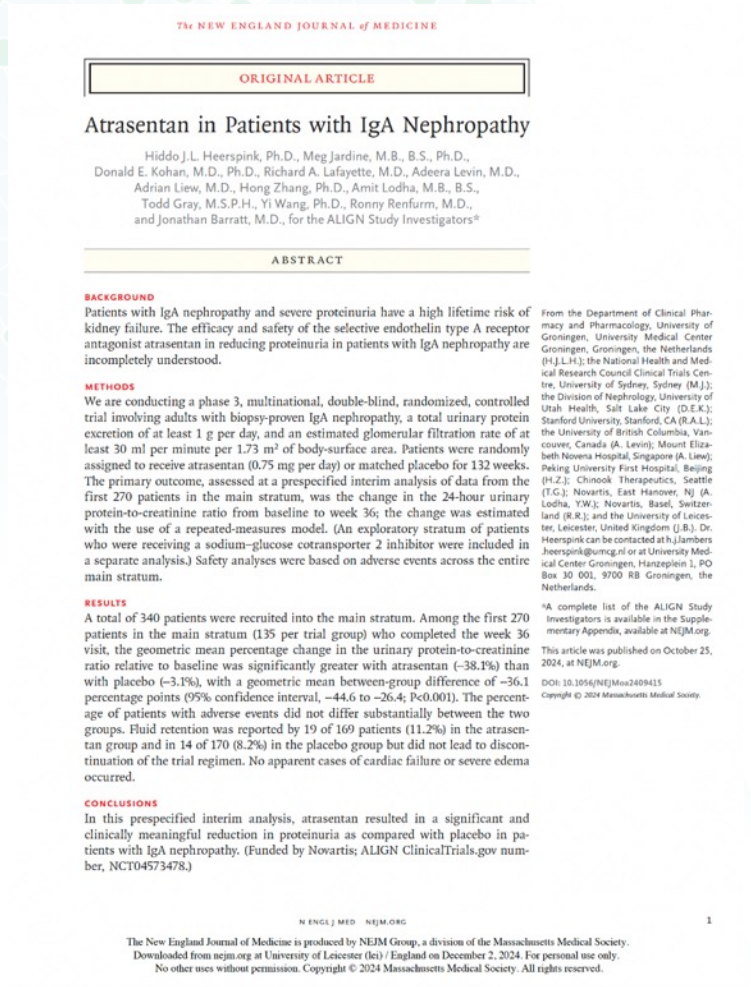
Last Update Posted 2024-05-23



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atrasentan in Patients with IgA Nephropathy

Hiddo J.L. Heerspink, Ph.D., Meg Jardine, M.B., B.S., Ph.D., Donald E. Kohan, M.D., Ph.D., Richard A. Lafayette, M.D., Adeera Levin, M.D., Adrian Liew, M.D., Hong Zhang, Ph.D., Amit Lodha, M.B., B.S., Todd Gray, M.S.P.H., Yi Wang, Ph.D., Ronny Renfurm, M.D., and Jonathan Barratt, M.D., for the ALIGN Study Investigators*

ABSTRACT

BACKGROUND

Patients with IgA nephropathy and severe proteinuria have a high lifetime risk of kidney failure. The efficacy and safety of the selective endothelin type A receptor antagonist atrasentan in reducing proteinuria in patients with IgA nephropathy are incompletely understood.

METHODS

We are conducting a phase 3, multinational, double-blind, randomized, controlled trial involving adults with biopsy-proven IgA nephropathy, a total urinary protein excretion of at least 1 g per day, and an estimated glomerular filtration rate of at least 30 ml per minute per 1.73 m^2 of body-surface area. Patients were randomly assigned to receive atrasentan (0.75 mg per day) or matched placebo for 132 weeks. The primary outcome, assessed at a prespecified interim analysis of data from the first 270 patients in the main stratum, was the change in the 24-hour urinary protein-to-creatinine ratio from baseline to week 36; the change was estimated with the use of a repeated-measures model. (An exploratory stratum of patients who were receiving a sodium–glucose cotransporter 2 inhibitor were included in a separate analysis.) Safety analyses were based on adverse events across the entire main stratum.

RESULTS

A total of 340 patients were recruited into the main stratum. Among the first 270 patients in the main stratum (135 per trial group) who completed the week 36 visit, the geometric mean percentage change in the urinary protein-to-creatinine ratio relative to baseline was significantly greater with atrasentan (−38.1%) than with placebo (−3.1%), with a geometric mean between-group difference of −36.1 percentage points (95% confidence interval, −44.6 to −26.4; P<0.001). The percentage of patients with adverse events did not differ substantially between the two groups. Fluid retention was reported by 19 of 169 patients (11.2%) in the atrasentan group and in 14 of 170 (8.2%) in the placebo group but did not lead to discontinuation of the trial regimen. No apparent cases of cardiac failure or severe edema occurred.

CONCLUSIONS

In this prespecified interim analysis, atrasentan resulted in a significant and clinically meaningful reduction in proteinuria as compared with placebo in patients with IgA nephropathy. (Funded by Novartis; ALIGN ClinicalTrials.gov number, NCT04573478.)

From the Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands (H.J.L.H.); the National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Sydney (M.J.); the Division of Nephrology, University of Utah Health, Salt Lake City (D.E.K.); Stanford University, Stanford, CA (R.A.L.); the University of British Columbia, Vancouver, Canada (A. Levin); Mount Elizabeth Novena Hospital, Singapore (A. Liew); Peking University First Hospital, Beijing (H.Z.); Chinook Therapeutics, Seattle (T.G.); Novartis, East Hanover, NJ (A. Lodha, Y.W.); Novartis, Basel, Switzerland (R.R.); and the University of Leicester, Leicester, United Kingdom (J.B.). Dr. Heerspink can be contacted at h.j.lambers.heerspink@umcg.nl or at University Medical Center Groningen, Hanzeplein 1, PO Box 30 001, 9700 RB Groningen, the Netherlands.

*A complete list of the ALIGN Study Investigators is available in the Supplementary Appendix, available at NEJM.org.

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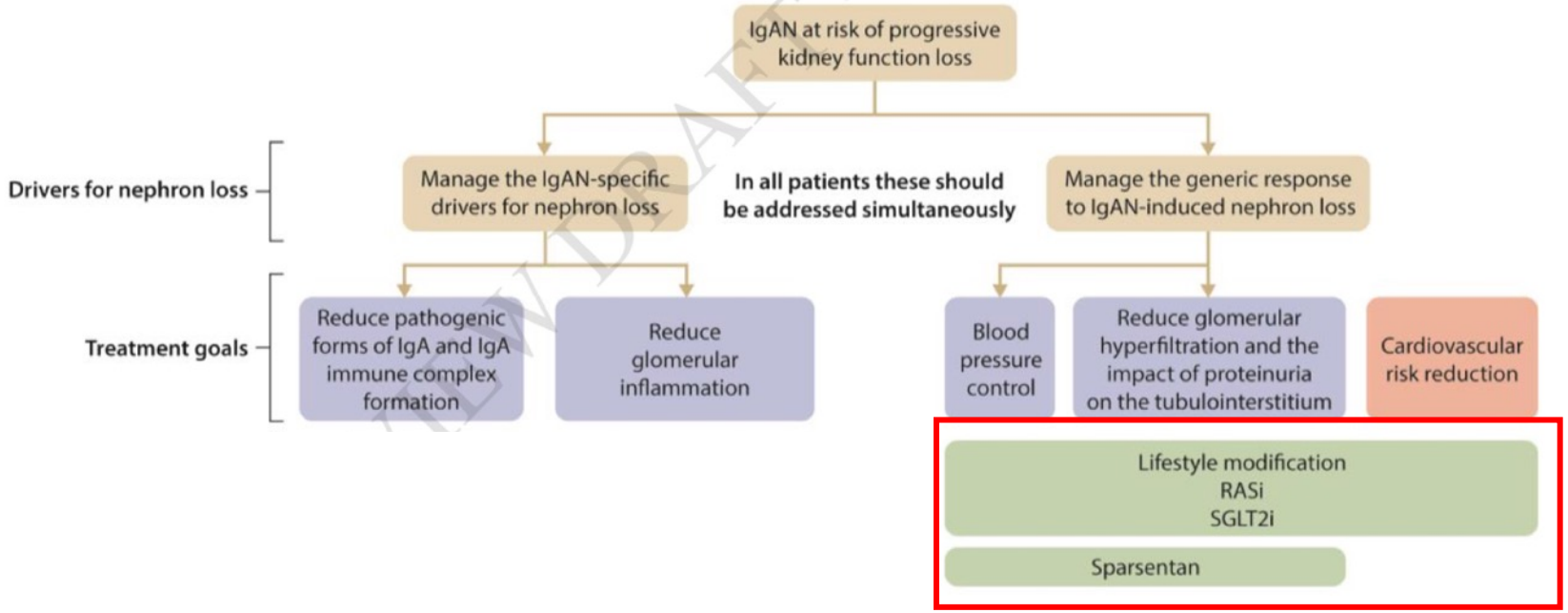


Figure 3 | Treatment targets in immunoglobulin A nephropathy (IgAN) and available to-date approved treatment options. *Measures to reduce glomerular hyperfiltration and the impact of proteinuria on the tubulointerstitium, using singly or in combination, renin-angiotensin system (RAS) blockade sparsentan, and sodium-glucose cotransporter-2 inhibition (SGLT2i). RASi, renin-angiotensin system inhibitors.

RECRUITING

A Study to Investigate Safety and Effect of Sparsentan in Combination With SGLT2 Inhibition in Participants With IgAN (SPARTACUS)

ClinicalTrials.gov ID NCT05856760

Sponsor Travere Therapeutics, Inc.

Information provided by Travere Therapeutics, Inc. (Responsible Party)

Last Update Posted 2024-02-23

RECRUITING

Randomized, Double-blind, Placebo-controlled, Crossover Study of Atrasentan in Subjects With IgA Nephropathy (ASSIST)

ClinicalTrials.gov ID NCT05834738

Sponsor Chinook Therapeutics, Inc.

Information provided by Chinook Therapeutics, Inc. (Responsible Party)

Last Update Posted 2024-04-19

RECRUITING

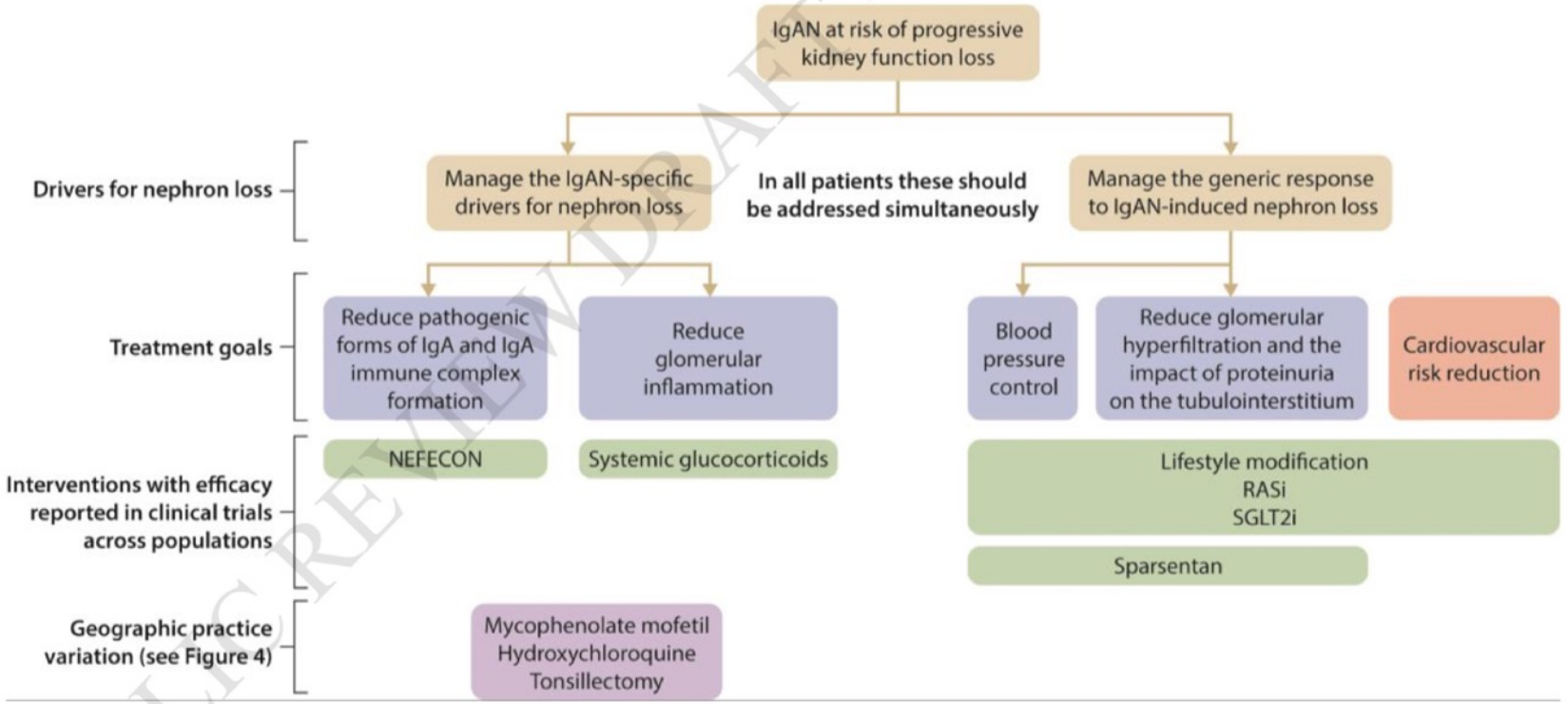
Study to Investigate Efficacy, Safety, and Tolerability of Zibotentan/Dapagliflozin Compared to Dapagliflozin in Participants With Chronic Kidney Disease and High Proteinuria (ZENITH High Proteinuria)

ClinicalTrials.gov ID NCT06087835

Sponsor AstraZeneca

Information provided by AstraZeneca (Responsible Party)

Last Update Posted 2024-04-23



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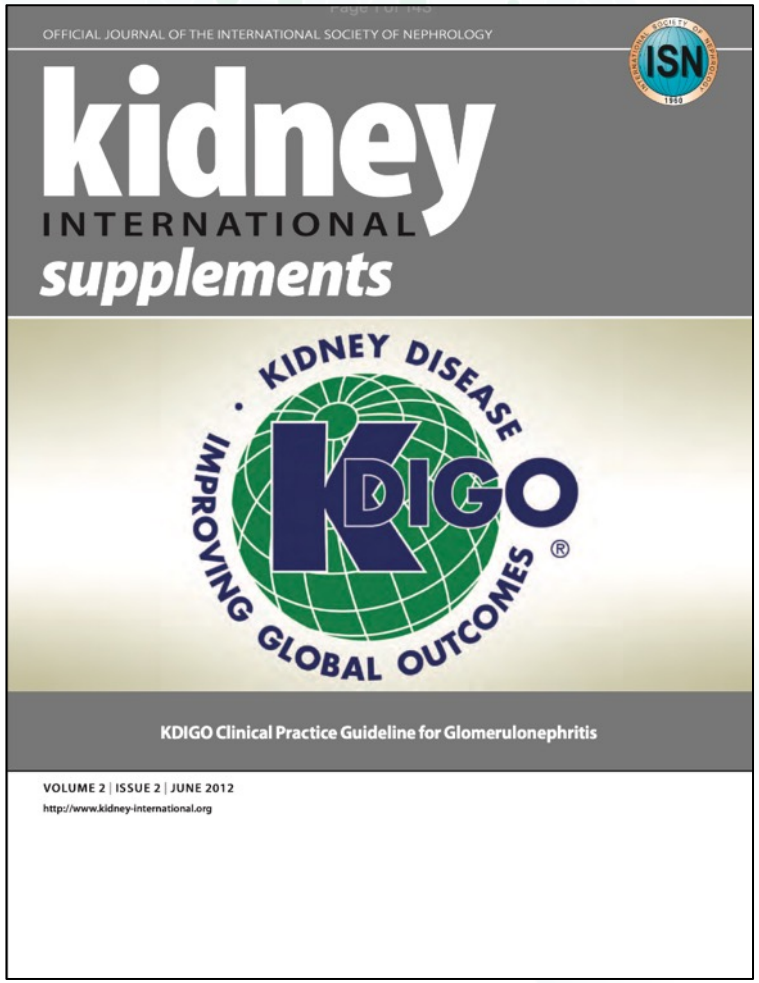
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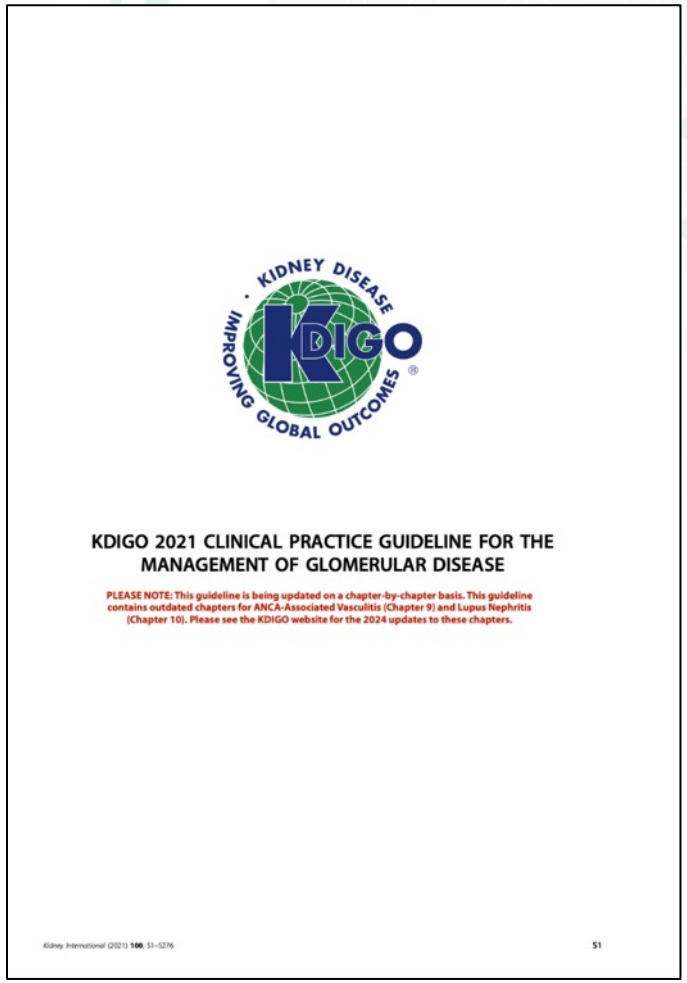
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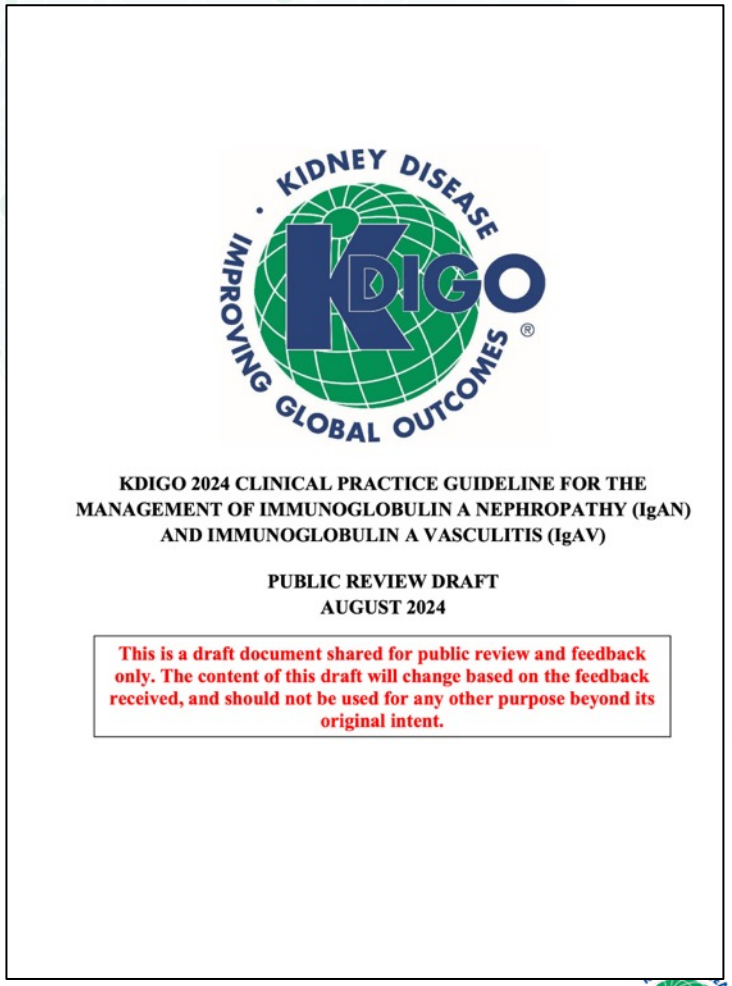
PLEASE NOTE: This guideline is being updated on a chapter-by-chapter basis. This guideline contains outdated chapters for ANCA-Associated Vasculitis (Chapter 9) and Lupus Nephritis (Chapter 10). Please see the KDIGO website for the 2024 updates to these chapters.
Kidney International (2021) 100, S1–S276
S1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