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Therapies on the Horizon for Diabetic Kidney Disease

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Abstract

Diabetic nephropathy is rapidly becoming the major cause of end-stage renal disease and cardiovascular mortality worldwide. Standard of care therapies include strict glycemic control and blockade of the renin-angiotensin-aldosterone axis. While these treatments slow progression of diabetic nephropathy, they do not arrest or reverse it. Newer therapies targeting multiple molecular pathways involved in renal inflammation, fibrosis, and oxidative stress have shown promise in animal models. Subsequently, many of these agents have been investigated in clinical human trials with mixed results. In this review, we will discuss recent findings of novel agents used in the treatment of diabetic nephropathy.

Keywords

Diabetic nephropathy; Bardoxolone; TGF-β; JAK/STAT

Introduction

The global incidence of diabetes has been increasing exponentially. In 2013, approximately 387 million people were affected by diabetes, and 90 % of these cases were reported to be due to type 2 diabetes mellitus [1]. Diabetes is a significant cause of mortality. An estimated 1.5–5.1 million deaths per year are attributed to diabetic complications, making diabetes the 8th leading cause of death. Since the introduction of insulin in 1923, the incidence of death from sepsis and hyperglycemia has dropped dramatically. Today, the leading cause of death in patients with diabetes is the direct result of diabetic complications, including macrovascular and microvascular events. Diabetic nephropathy develops in one third of all diabetic patients and is associated with significant cardiovascular mortality and end-stage renal disease. A staggering 42 % of patients with end-stage renal disease (ESRD) in the USA have diabetic nephropathy [2].

The typical clinical course of diabetic nephropathy is predictable. It progresses from microalbuminuria (urine albumin excretion rate (UAER) 30–300 mg/24 h) to

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Compliance with Ethical Standards

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macroalbuminuria (UAER≥300 mg/24 h) and eventually renal dysfunction leading to ESRD. However, some patients develop progressive renal dysfunction in the presence of either normoalbuminuria or microalbuminuria [3]. Regardless, microalbuminuria is a strong predictor of cardiovascular mortality and morbidity in diabetic patients [4].

Pathological changes of diabetic nephropathy include thickening of glomerular basement membrane, thickening of tubular basement membrane, mesangial expansion, focal and global glomerulosclerosis, and tubulointerstitial fibrosis.

Extracellular matrix expansion appears to be an early and key change in diabetic nephropathy that leads to subsequent glomerular sclerosis and scarring and podocyte detachment. The pathophysiology underlying development of diabetic nephropathy and other complications has recently been reviewed in depth [5].

Traditional interventions, such as blood pressure control with renin-angiotensin-aldosterone system (RAAS) blockade and glycemic control, have been shown to slow progression of chronic kidney disease (CKD) [6]. However, progression to ESRD is still common. We are now learning that the etiology of diabetic nephropathy is multifactorial and includes genetic factors, activation of the renin-angiotensin aldosterone system, and pathways of renal fibrosis and oxidative stress. Animal models exploring the contribution of these molecular pathways have shown promising results for potential targets to treat and prevent diabetic nephropathy. In this review, we will discuss current as well as novel therapies targeting various molecular pathways involved in diabetic nephropathy.

Standard Therapy and RAAS System

Large studies have demonstrated that intensive glycemic control slows the progression of diabetic nephropathy. The Diabetes Control and Complications Trial (DCCT) of 1441 type 1 diabetes patients demonstrated that a strict glycemic target of 7.3 vs 9.1 % is associated with decreased rates of microalbuminuria, macroalbuminuria, and renal insufficiency [7]. Furthermore, strict glycemic control appeared to impart a “metabolic memory” in patients, as remote strict control slowed progression rates several years after the intervention. The United Kingdom Prospective Diabetes Study (UKPDS) of 3867 newly diagnosed type 2 diabetes patients also demonstrated that intensive glycemic control reduced microalbuminuria by 3 % [8].

Blood pressure control by RAAS blockade and other anti-hypertensive agents also show beneficial outcomes and are central to management of diabetic patients. The UKPDS study demonstrated every 10 mmHg reduction in systolic blood pressure translated to a reduction in diabetes complication and death by 12 and 15 %, respectively [8]. The use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB) are currently the standard of care to reduce proteinuria, control blood pressure, and prevent progression of diabetic nephropathy.

Dual blockade of renin-angiotensin system (RAS) with angiotensin-converting enzyme inhibitors (ACEi) and ARBs is not recommended by Kidney Disease Outcome Quality Initiative (KDOQI), Kidney Disease Improving Global Outcomes (KDIGO), or American

Diabetes Association (ADA) guidelines [9–11]. The Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) trial and the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) did not show any benefit of combination ACEi and ARB therapy [12, 13], which was associated with a higher incidence of adverse events. The addition of a direct renin inhibitor, aliskerin, in the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) did not show any benefit in the primary endpoint of ESRD; however, this trial did show improvement in albuminuria and resulted in a lower blood pressure [14].

Spironolactone, a mineralocorticoid receptor blocker, has also been studied in the prevention of diabetic nephropathy progression. Aldosterone via its stimulatory action on the mineralocorticoid receptor results in increased sodium reabsorption and is also believed to have direct proinflammatory and profibrotic effects. Mineralocorticoid receptor antagonists have been shown to have antiproteinuric effects as adjuvant therapy to RAS blockade in diabetic kidney disease. However, there is increased risk of hyperkalemia with concurrent RAS inhibitor use [15–17]. The PRIORTY randomized trial is ongoing to evaluate the efficacy of spironolactone when added to RAS blockers in 3500 patients with diabetes and albuminuria.

There is evidence to suggest there may be blood pressure independent renoprotective benefits of RAS blockade including inhibition of profibrotic factors such as transforming growth factor-β (TGF-β). However, maximizing ACEi or ARB therapy does not provide additional benefits, and thus, alternative novel therapies are urgently needed.

Therapies on the Horizon

Novel approaches targeting molecular pathways involved in renal inflammation, fibrosis, and oxidative stress have been or are currently being evaluated as potential therapies for diabetic nephropathy.

Bardoxolone Methyl

Bardoxolone methyl is a semisynthetic oleanane triterpenoid compound that possesses antioxidant properties through activation of nuclear factor erythroid derived 2 (Nrf-2) and inhibition of nuclear factor (NF)-κβ. Activation of NF-kβ promotes oxidative stress and is proinflammatory [18]. The Nrf2 pathway is constitutively active and becomes upregulated in response to oxidative stress resulting in increased transcription of downstream gene targets. Synthetic triterpenoid bardoxolone methyl (CDDO-Methyl ester) is a potent inducer of the Nrf2/Keap1 pathway, which leads to Nrf2 translocation into the nucleus to upregulate antioxidant and cytoprotective genes. Bardoxolone methyl also has anti-inflammatory properties through its inhibition of the IKKβ/NF-kβ signaling pathway. Treatment with a bardoxolone methyl analog led to a reduction in glomerulosclerosis, interstitial fibrosis, and inflammation in rat models with CKD induced by 5/6 nephrectomy [19].

The Bardoxolone Methyl Treatment: Renal Function in CKD/Type 2 Diabetes (BEAM) trial was a phase II, double-blind, randomized trial of 227 patients with type 2 diabetes mellitus and estimated glomerular filtration (eGFR) 20–45 designed to evaluate bardoxolone. All

three doses of bardoxolone (25, 75, or 150 mg) resulted in increased eGFR in comparison to the placebo group at 24 weeks. This improvement in eGFR persisted for 52 weeks [20]. However, the medication was noted to cause an increase in albuminuria and adverse effects, such as massive weight loss, muscle spasms, hypomagnesaemia, elevations in alanine aminotransferase levels, and gastrointestinal symptoms.

The Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes Mellitus (BEACON) trial was a phase III, multicenter, randomized, double-blind study designed to evaluate the efficacy of bardoxolone 20 mg daily in 2185 patients with stage IV CKD (eGFR 15–30 ml/min/1.73 m^2) [21]. However, the study was terminated early in October 2012 due to safety concerns with an increased incidence of cardiovascular events and heart failure. At the median time point of 9 months, there was increased eGFR in the treatment group, but no difference in progression to ESRD between the bardoxolone and placebo groups. Efforts are ongoing to investigate potential mechanisms for the negative results from the BEACON trial.

Pentoxyfylline

Pentoxifylline, a methylxanthine derivative and non-specific phosphodiesterase inhibitor with anti-inflammatory, anti tumor necrosis factor α (TNFα), and anti-fibrotic properties, is used clinically to treat peripheral arterial disease. A recent meta-analysis of 10 studies involving 476 patients with diabetic nephropathy demonstrated a decrease in proteinuria at a median duration of treatment of 6 months when pentoxyfylline was compared to placebo; both groups received standard of care (ACEi or ARB) [22]. The Pentoxifylline for Renoprotection in Diabetic Nephropathy (PREDIAN) trial was a randomized controlled clinical trial evaluating pentoxifylline use with adjunctive RAS blockade in 169 type 2 diabetes patients with diabetic nephropathy and CKD stage 3–4. This trial demonstrated that the group treated with pentoxifylline exhibited a smaller decline in eGFR and greater reduction in albuminuria over 24 months. There was a significant mean difference of 4.3 ml/min/1.73 m^2 in the reduction of eGFR between the pentoxifylline and placebo group; the results became statistically significant at 1 year demonstrating the need for prolonged therapy [23•].

A study of 66 patients with proteinuric CKD (eGFR 10–60 ml/min/1.73 m^2) in Taiwan compared pentoxifylline therapy with losartan to placebo and losartan and demonstrated a 23 % reduction in proteinuria in the pentoxifylline group in comparison to 13.8 % increase in proteinuria in the placebo group over 1 year [24]. The rate of eGFR decrease was significantly lower in the pentoxifylline group with a mean difference of −5.1 ml/min/1.73 m^2 per year. The study only included 16 patients with diabetic nephropathy. Pentoxyfylline appears to have favorable results in diabetic nephropathy and non-diabetic CKD. While the preliminary data are promising, larger, blinded, placebo-controlled randomized trials are needed.

Ruboxistaurin, PKC Beta Inhibitor

Ruboxistaurin mesylate (previously known as LY333531) is a selective PKC-βI and -βII inhibitor. Protein kinase C (PKC) comprises a family of 12 serine-threonine protein kinases

that play important roles in intracellular signal transduction. Hyperglycemia, the central problem in diabetes, leads to increased diacylglycerol, advanced glycation end products, and oxidative stress leading to PKC hyperactivity [25]. In animal models of diabetic nephropathy, ruboxistaurin has been shown to normalize glomerular hyperfiltration, reduce albuminuria, TGF-β, and extracellular matrix (ECM) proteins and has been shown to decrease expansion of the mesangium, glomerulosclerosis, and tubulointerstitial fibrosis [26].

Ruboxistarin has been assessed in clinical trials of diabetic nephropathy, retinopathy, and neuropathy. In a pilot phase 2, randomized, double-blind, placebo-controlled study, 123 patients with diabetic nephropathy and albuminuria were treated with ruboxistaurin 32 mg daily for 1 year. The ruboxistaurin group demonstrated significant reduction in albuminuria, no increase in urinary TGF-β, and stable level of eGFR [27, 28]. In comparison, patients treated with placebo did not have a reduction in albuminuria and were noted to have a decline in eGFR and increased urinary TGF-β. All patients had received a stable dose of ACEi and/or ARB during the previous 6 months, which was continued during the study. Of note, women and men with serum creatinine >1.7 and 2.0 mg/dl were excluded, respectively.

Longer duration studies have evaluated use of ruboxistaurin in patients with diabetic retinopathy over a median follow-up of 3 years. These studies demonstrated reduced risk of vision loss in patients with moderate to severe retinopathy. Many of these studies did not measure baseline albuminuria. At the end of study, the rates of albuminuria did not differ between the treatment groups nor were there any significant changes in eGFR or clinical endpoints (doubling of serum creatinine, progression to CKD stage 4 and 5, or death) [29]. Of note, the kidney function at the beginning of these retinopathy trials was normal. Ruboxistaurin was well tolerated overall. Another study evaluating use of ribuoxistarin in diabetic neuropathy was terminated early due to futility of treatment [30]. These studies show promising results that ruboxistaurin may be used in prevention of diabetic nephropathy. However, longer duration and larger studies are needed to further evaluate efficacy and role in progression of CKD.

Pirfenidone, TGF-β Inhibitor

The TGF-β system is activated in diabetic nephropathy and plays a role in extracellular matrix accumulation, inflammation, and scarring. Pifrenidone, a TGF-β inhibitor with anti-fibrotic properties, has been shown to decrease TGF-β and reduce matrix accumulation in animal models of kidney disease. An open label clinical study of patients with focal segmental glomerulosclerosis demonstrated 25 % reduction in rate of eGFR decline in patients treated with pirfenidone [31]. A pilot, small-scale study of pirfenidone in 77 diabetic nephropathy patients with eGFR 20–75 ml/min/1.73 m^2 demonstrated improved renal function in the pirfenidone treated group. The study demonstrated increase in mean eGFR in pirfenidone 1200 mg/dl group (+3.3±8.5 ml/min per 1.73 m^2), whereas the mean eGFR decreased in the placebo group (−2.2+−4.8 ml/min/ 1.73 m^2; P=0.026 versus pirfenidone at 1200 mg/d). The higher dose pirfenidone 2400 mg group demonstrated non-significant result in eGFR and high dropout rate (11 of 25) [32]. These are small clinical

studies that show promise as a potential therapy to prevent progression of diabetic nephropathy, but larger studies are needed to further evaluate efficacy.

Bindarit, MCP-1/CCL2 Inhibitor

Glomerulosclerosis in diabetic nephropathy is characterized by deposition of ECM matrix protein and ECM remodeling leading to renal insufficiency and proteinuria. Growth factors and cytokines released by glomerular cells and leukocytes play a role in this process. Among them, MCP-1/CCL2 has been shown to correlate with glomerular damage and albuminuria in diabetic nephropathy. In a mouse model of type 1 diabetic nephropathy, blocking CCR2 receptor reduces glomerular deposition of TGF-β1 and type IV collagen and mesangial matrix expansion [33, 34].

Bindarit has selective inhibitory effect on the synthesis of monocyte chemotactic protein (MCP) subfamily of CC inflammatory chemokines, including MCP-1/CCL2, MCP-3/CCL7, and MCP-2/CCL8. A small, double-blind, randomized study of 73 type 2 diabetic patients with albuminuria on stable irbesartan therapy was randomized to 12 weeks of therapy with bindarit and subsequently followed for 4 weeks after treatment withdrawal. Bindarit significantly and safely reduced albuminuria in the bindarit group, but UAE values recovered to baseline with withdrawal of therapy [35]. Bindarit therapy in lupus nephritis has been shown to reduce UAE and urinary CCL2 levels [36]. These preliminary data support bindarit as a promising candidate therapy for diabetic nephropathy. A 12-month pilot, phase II, double-blind, randomized study evaluating bindarit therapy in comparison to placebo therapy with irbesartan use in patients with diabetic nephropathy has been completed; the results of this study have not yet been published.

Sulodexide

Preclinical data in experimental animal models showed promising results for glycosaminoglycans (GAGs) to prevent the development of diabetic nephropathy. In streptozotocin-induced diabetic mice, administration of GAG prevented structural changes in the glomerular basement membrane, ECM expansion, and albumin excretion rate associated with diabetic nephropathy. GAGs are believed to repair the deranged ECM in diabetes by normalizing the sulfation and synthesis of proteoglycans and diabetes induced increase in type IV collagen [37, 38, 39•, 40]. The proposed mechanism is inhibition of TGF-β1 synthesis in diabetic nephropathy as well as inhibition of heparinase. Levels of heparinase, expressed by podocytes and proximal tubular cells, are increased in diabetic conditions leading to derangements in glomerular permeability, tubular and interstitial fibrosis, and vascular permeability [41].

Sulodexide, an oral formulation, is composed of two GAGs (80 % fast moving heparin and 20 % dermatan sulfate). Sulodexide has been shown to reduce micro- and macroalbuminuria in both type 1 and type 2 diabetic patients. In 2002, the Diabetic Nephropathy and Albuminuria Sulodexide (Di.N.A.S), a multicenter, randomized, placebo-controlled study evaluated three different doses of sulodexide (50, 100, and 200 mg) for 4 months followed by a 4-month washout period. There was a 40 % reduction in albuminuria in the 200 mg

group [42]. Sulodexide was effective for both type 1 and type 2 diabetes mellitus with and without concomitant ACEi use.

Two subsequent studies undertaken by the Collaborative Study Group, the SUN-micro and SUN-macro trials, did not show benefit with sulodexide use. The SUN-micro trial which was a phase III trial of 1056 microalbuminuric diabetes mellitus type 2 patients over a 12-month period on maximal dose of ACEi/ARB did not show a difference between the treatment (sulodexide 200 mg daily) and control groups [43]. The SUN-macro trial, which enrolled type 2 diabetic patients with overt diabetic nephropathy, was terminated early due to inconclusive results of the SUN-micro trial [44].

Although the SUN-micro trial did not show any benefit, there is some thought these patients may have more advanced CKD. There was also concern that since sulonex was produced by a different company then the original sulodexide (Vessel) used in all the prior trials, and there may have been a difference in gastrointestinal absorption or pharmacological activity. This class of medications may need more trials to further evaluate effect.

Endothelin Receptor Antagonists

Endothelins are small vasoactive peptides with pleiotropic actions that promote hypertension, albuminuria, inflammation, and endothelial dysfunction. Endothelin 1 activates endothelin 1 receptor (ETA) and endothelin 2 receptors (ETB1 and ETB2). A phase II placebo-controlled trial of the ETA blocker avosentan (dose range 5–50 mg) in 286 type 2 diabetes patients with albuminuria demonstrated significant reduction in urine albumin to creatinine ratio (UACR) at week 12 [45]. Twelve percent of patients experienced peripheral edema in the higher dose groups (≥25 mg). The ASCEND phase III, controlled trial of avosentan (25 mg or 50 mg) versus placebo in 1392 type 2 diabetes patients with adjuvant RAS blockade demonstrated 44 and 49 % reduction in albuminuria, respectively [46]. However, the study was terminated early at 4 months due to increased cardiovascular and congestive heart failure events and mortality in the avosentan group. Atrasentan, another selective ETA blocker has also shown promising results in a phase II trial [47]. Peripheral edema was also observed with atrasentran use. There is an ongoing phase III trial, the Study Of Diabetic Nephropathy With Atrasentan (SONAR), to assess atrasentan versus placebo in patients with type 2 diabetes, eGFR 25–75 ml/min/1.73 m^2, and UACR 300–5000 mg/g. Patients with history of peripheral edema, congestive heart failure, or pulmonary disease are not eligible to enroll; this trial is expected to be completed in February 2017.

Allopurinol

Studies have shown that uric acid may be a factor in development of diabetic nephropathy. The Joslin Kidney Study evaluated predictors of GFR loss in 355 non-proteinuric type 1 diabetes patients and demonstrated there is a significant increased risk of loss of GFR associated with increased uric acid levels; the relative risk of developing increased GFR loss is 1.5 (95 % CI 1.3–1.9, p=0.002) for each mg/dl increase in serum uric acid. Patients with type 2 diabetes also have increased risk of renal progression with hyperuricemia [48]. The mechanism for this is unclear but believed to be related to alterations in nitric oxide pathway, induction of proinflammatory cytokines, and increased oxidative stress [49]. Two small

clinical trials have shown favorable outcomes with allopurinol treatment in patients with CKD (with and without diabetes) and proteinuria [50, 51]. The Preventing Early Renal Function Loss in Diabetes (PERL) study is an ongoing 3-year international, randomized, double-blind, placebo control trial to evaluate the use of allopurinol in 400 type 1 diabetic patients with micro- and macroalbuminuria and GFR 45–100 ml/min/1.73 m^2 [52].

Vitamin D Receptor Activators

In animal models, vitamin D deficiency is associated with increased proteinuria, and treatment with VDR activators calcitriol and paricalcitol improves proteinuria [53]. The selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetic nephropathy (VITAL) study, a phase III randomized control trial, investigated the use of paricalcitol (1 or 2 μg) with RAS blockade in 281 patients with type 2 diabetes and stage 2–4 CKD. There was no significant difference in percentage change in UACR at 24 weeks between the groups. There was a significant change in 24 h albuminuria (a secondary outcome) at 24 weeks in the 2 μg paricalcitol group [54]. However, the higher dose was poorly tolerated due to parathyroid hormone suppression. Though non-significant, there was also a concerning, reversible decrease in eGFR by 5 % and incidence of ESRD and death was 6.6-fold higher in the 2 μg dose group than in placebo. The Salt Intake and Antiproteinuric Effect of Paricalcitol in Type 2 Diabetes (PROCEED) trial is an ongoing placebo-controlled trial evaluating the antialbuminuric effects of paricalcitol 2 μg in type 2 diabetes for 4 months.

Targeting the Vasculature

Over the past decade, great advances have been made in the understanding and treatment of diabetic eye complications. Elevated levels of the vascular endothelial growth factor (VEGF) are linked to macular edema and proliferative retinopathy. The Food and Drug Administration (FDA) has approved the use of anti-angiogenic agents including bevacizumab, ranizibumab (Lucentis and Avastin), and aflibercept (Eyelea) that target the VEGF ligand to treat diabetic macular edema [55]. These agents provide improvement in visual acuity and reduction of retinal edema. It has long been recognized that diabetic retinopathy and nephropathy often occur together in the same patient. Indeed, the underlying pathophysiology is believed to be similar, and elevated VEGF signaling has been linked to neoangiogenesis at the vascular pole of the glomerulus early in the course of diabetic nephropathy. However, glomerular VEGF expression is reduced late in the course of diabetic nephropathy. This reduction coincides with loss of healthy podocytes, which are the major source of renal VEGF. Furthermore, VEGF inhibitors are linked to thrombotic microangiopathy in the kidney and thus, cannot be used to treat diabetic nephropathy.

Alternate strategies to target the vasculature are more promising for diabetic nephropathy. The angiopoietin-Tie2 pathway was the second tyrosine kinase vascular pathway identified, and inhibition of this pathway is linked to adverse cardiovascular outcomes in diabetes and to worsened diabetic nephropathy in animal models [56]. A pilot study using AKB-9778, a small molecule inhibitor that activates Tie2, was shown to be safe for patients with diabetic macular edema [57]. The drug targets the phosphatase VE-PTP (HPTPb), which dephosphorylates Tie2. Animal models support a role for reduced angiopoietin-Tie2

signaling in diabetic nephropathy [56, 58], making it an attractive target for intervention. It is hoped that AKB-9778 will improve microvascular complications in both the retina and the kidney through increased Tie2 activation.

Other Targets Under Clinical Investigation

NOX Inhibition

Additional therapies are currently under evaluation in clinical trials. A large amount of data suggests that increased reactive oxygen species promote diabetic nephropathy [59]. Inhibition of nicotinamide adenine dinucleotide (NADPH) oxidase improves renal function in diabetic mouse models, presumably through reduction of generation of reactive oxygen species (ROS). Knockout mice for 2 of the Nox enzymes (Nox1 and Nox4) are protected from diabetic nephropathy [60]. The specific NOX1/NOX4 inhibitor GKT137831 is currently being tested in type 2 diabetes subjects with albuminuria (clinical trials.gov number, NCT02010242).

JAK/STAT Pathway Inhibition

At the American Diabetes Association meeting in Boston, 2015, a poster was presented reporting promising early results in patients with diabetes and albuminuria treated with a JAK/ STAT pathway inhibitor—baricitinib. Activation of members of the JANUS kinase family of signal transducers (JAK) and the latent signal transducers of activated transcription (STAT) have been observed in cells and glomeruli exposed to high glucose and angiotensin II as well as in biopsies from patients with diabetic nephropathy [61–63]. Furthermore, inhibition of JAK/STAT pathway showed improvement in a rat model of diabetes [64]. A clinical trial is currently underway (clinical trials.gov number, NCT01683409).

Conclusion

Diabetic nephropathy is a multifactorial disease process involving the renin-angiotensin pathway as well as molecular pathways involved in upregulation of extracellular matrix components, reactive oxygen species, and renal fibrosis. Standard therapy with strict glycemic control and ACEi/ARB has not been shown to arrest or reverse progression to ESRD, although it has led to slowed progression. However, since the introduction of RAS blockade ~20 years ago, there have not been any great advances in treatment of diabetic nephropathy. Novel agents targeting specific molecular pathways at the cellular level have shown promise in animal models of diabetes. Some therapies such as pentoxyfylline, ruboxistaurin, and bindarit have also shown promising initial results in treatment of diabetic nephropathy in patients. Initially, sulodexide treatment was shown to be beneficial, but the most recent trial showed surprisingly poor results. There are ongoing trials evaluating the use of active vitamin D analog, allopurinol, and endothelin receptor antagonists in diabetic nephropathy to improve albuminuria and renal progression.

Despite significant new insights regarding the pathogenesis of diabetic nephropathy, treatment options remain limited. In many instances, promising therapies in preclinical animal models have performed poorly in clinical trials. There are several reasons for the difficulty in translating experimental benefits to the clinic. First, animal models are

imperfect representations of disease in patients. While there has been substantial effort invested to develop improved rodent models of diabetic complications, many classic features of diabetic nephropathy are not recapitulated in models. Second, the pathogenesis of diabetic nephropathy is multifactorial and diabetic nephropathy is a heterogeneous disease. Development of “smart trials” designed to enroll patients who have been precisely phenotyped and stratified based on underlying etiology and risk factors may provide better results. Third, the natural history of diabetic nephropathy is also a limiting factor. The long time needed to demonstrate progression requires a major investment by pharmaceutical companies and investigators.

Although there are challenges, identification of novel therapies to slow and or arrest progression of diabetic nephropathy provides a great opportunity to impact global health. Further studies to elucidate underlying mechanisms, improved methods to phenotype and stratify patients at an early stage of disease and studies aimed at identifying “protective” factors in patients will all help in the discovery of new therapies. Finally, joining forces with networks that already exist and are well poised to perform intervention studies in large groups of patients—such as the Diabetic Retinopathy Clinical Research Consortium (DRCR)—may facilitate much needed clinical trials in patients with diabetic nephropathy.

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