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The Future: Experimental Therapies for Renal Disease in Diabetes

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Abstract
Diabetic nephropathy is the commonest cause of end-stage renal disease and affects between 30 and 45% of patients with diabetes mellitus. There is no cure for diabetic nephropathy and the current management of this condition includes glycaemic control, blockade of the renin-angiotensin aldosterone system and lifestyle changes. However, many patients eventually progress to end-stage renal disease. The exact pathogenesis of diabetic nephropathy is still being researched, and recent advances have led to the development of several novel potential therapeutic targets. There are a number of different experimental therapies that are currently being assessed. Generally, these can be separated into drugs targeting vasculature/haemodynamic effects, drugs targeting inflammation and drugs targeting oxidative stress. Drugs targeting the vasculature include Tie-2 activators, sodium-glucose transport protein 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) agonists. Anti-inflammatory therapies include inflammatory cytokines inhibitors, pentoxifylline, as well as anti-transforming growth factor α/epiregulin therapies. Finally, anti-oxidative stress therapies include nicotinamide adenine dinucleotide phosphate (NADPH) oxidase inhibitors and allopurinol. Many new trials are providing promising results and it is likely that some of these therapies will be available for clinical use within the next decade. This article will seek to outline the main advancements in each of these experimental therapies for diabetic nephropathy. ***Results:*** Abnormal vascular remodelling, inflammation and oxidative stress seem to be the 3 main sources from which future new drugs for diabetic kidney disease will originate.

Background

Diabetic nephropathy (DN), one of the most devastating diabetic chronic complications, is the commonest cause of end-stage renal disease. The complex pathogenesis affects both the glomerulus and tubules: in the glomeruli, we observe mesangial expansion, impairment of glomerular endothelial cell function and loss of podocytes, and in the tubular compartment, inflammatory-driven interstitial fibrosis [1]. These pathological changes

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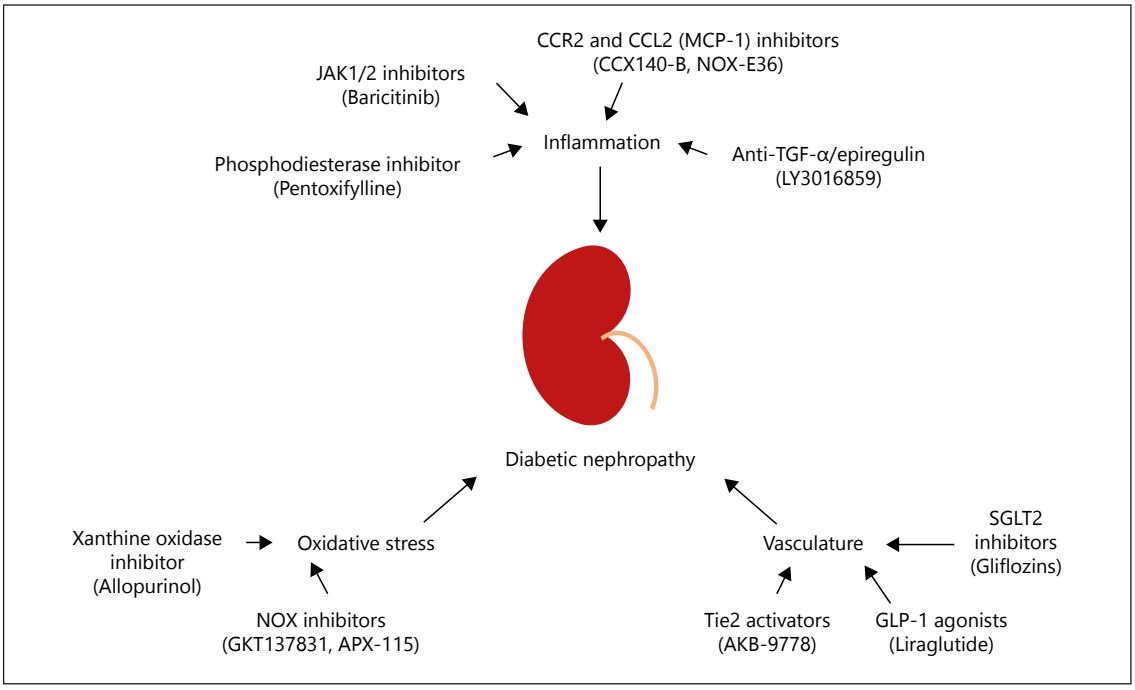

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Fig. 1. Overview of future experimental therapies in DN.

contribute to the clinical manifestations of DN that manifests with proteinuria, raised serum creatinine and a progressive decline in renal function. There is no cure available for DN and current management relies on the blockade of the renin-angiotensin aldosterone system (RAAS), glycaemic and lipid control, and lifestyle changes. These therapies aim to slow progression of the disease although eventually many patients reach end-stage renal disease requiring renal replacement therapy.

There is a clear need for new effective therapies in DN that will improve kidney function, reduce disease progression and eventually improve kidney survival. Many experimental therapies are currently being researched. These can be broadly separated into drugs that affect vasculature, anti-inflammatory agents and drugs targeting oxidative stress. This article provides a brief overview of the most promising experimental therapies for DN (Fig. 1).

Drugs Targeting Vasculature

Tie-2 Activators

Dysregulation of vascular growth factors such as vascular endothelial growth factor (VEGF) and Angiopoietins (Angpt)-1 and -2 have been implicated in diabetic renal complications [1]. Currently, effective anti-VEGF therapies are available only for diabetic retinopathy and their use in DN in humans is yet to be established. Both Angpt1 and 2 compete for binding at the Tie-2 receptor, with Angpt1 activating downstream receptor signalling and Angpt2 acting as an antagonist. It has been suggested that an imbalance between Angpt1 and 2 (Angpt2>Angpt1) is involved in the pathogenesis of DN [1]. This has led to the development of drugs that sustain Tie-2 receptor activation such as AKB-9778, an inhibitor of vascular endothelial-protein tyrosine phosphatase (VE-PTP). Two recent trials have assessed the effect of AKB-9778 in patients with diabetic retinopathy [2] and have demonstrated clinical benefit when given in combination with ranibizumab, compared to ranibizumab monotherapy in diabetic retinopathy. There is evidence to suggest that growth factors such as the Angpt play a similar role in the pathogenesis of DN.

GLP-1 Agonists and SGLT2 Inhibitors

The importance of incretin mimetic such as GLP-1 analogues in diabetes is widely known. Indeed, GLP-1 analogues are an established therapy in diabetes known for their glucose-lowering properties and beneficial effects on blood pressure and weight. The recent randomised controlled trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results –

LEADER) demonstrated a cardioprotective role of liraglutide [3]; a secondary analysis of this study suggested that liraglutide treatment could significantly reduce renal outcomes of type 2 diabetes (T2DM) patients, in particular, the incidence of macroalbuminuria [4].

Similarly, the SGLT2 inhibitors have shown definite cardiovascular protection and a recent study has demonstrated a likely renoprotective role for this class of drugs (https://www.prnewswire.com/news-releases/phase-3-credence-renal-outcomes-trial-of-invokana-canagliflozin-is-being-stopped-early-for-positive-efficacy-findings-300681634.html?tc = eml_cleartime) [5].

Drugs Targeting Inflammation

C-C Chemokine Receptor Type 2 (CCR2) and Chemokine Ligand 2 (CCL2)/Monocyte Chemoattractant Protein 1 (MCP-1) Inhibitors

Inflammatory pathways are known to play a key role in the development and progression of DN [1]. The proinflammatory chemokine CCL2, also known as MCP1 has been implicated in the pathogenesis of DN and has therefore become a target for possible novel treatments. The CCR2 antagonist CCX140-B has been shown to have beneficial effects in DN both in animal models and clinical trials. Studies on diabetic mouse models have shown that CCX140-B improves albuminuria, insulin sensitivity and inflammatory macrophage numbers [6]. Additionally, a randomised clinical trial assessed the effects of CCX140-B on patients with T2DM and DN who were currently being treated with standard care (RAAS inhibition). This study showed that CCX140-B significantly lowered albuminuria in T2DM patients when added to current standard treatment [7].

Trials have also assessed the effects of direct inhibition of CCL2 using the drug known as NOX-E36. Mouse models treated with NOX-E36 have shown a reduction in albuminuria and beneficial effects on the glomerular endothelial glycocalyx [8]. A Phase 2 clinical trial has shown some renoprotective effects of NOX-E36 on albuminuria in patients with T2DM and DN [9].

Overall, the preliminary data on CCR2 and CCL2 blockade is promising, but long-term effects of these medications on renal outcomes and mortality are needed.

Janus Kinase 1/2 Inhibitors

The Janus kinase-signal Transducer and Activator of Transcription (JAK-STAT) pathway is involved in transmitting inflammatory signals and has been implicated in disease progression of DN. Baricitinib is an oral inhibitor of JAK1 and JAK2, enzymes that are involved in the JAK-STAT pathway. A recent phase 2 randomised clinical trial assessed the effects of varying doses of baricitinib on DN outcomes compared to a placebo [10]. This study demonstrated a significant reduction in albuminuria, as well as a reduction in inflammatory biomarkers such as CCL2. The main observed adverse reaction of baricitinib was anaemia, suggesting that despite its benefits, this drug may have a relatively narrow therapeutic window.

Pentoxifylline

Pentoxifylline is a phosphodiesterase inhibitor, licensed for the treatment of vascular disorders and is recognised for its anti-inflammatory properties. The Pentoxifylline for Renoprotection in Diabetic Nephropathy study assessed the effects of pentoxifylline alongside RAAS inhibition, on the progression of DN in T2DM patients with established DN [11]. The results demonstrated that pentoxifylline was associated with a significant reduction in renal function decline and albuminuria. The main adverse effects of the medication were gastrointestinal symptoms that mostly resolved without treatment. Larger, blinded, multi-centre studies with longer study periods are warranted to confirm the long-term effects of this therapy.

Anti-Transforming Growth Factor α (TGF-α) and Anti-Epiregulin

There is evidence to suggest that overstimulation of the epidermal growth factor receptor (EGFR) pathway is involved in the pathology of chronic kidney disease [1]. The EGFR ligands TGF-α and epiregulin are particularly important. As direct EGFR inhibitors have dermatological adverse reactions, a humanized monoclonal IgG4 antibody, LY3016859, has been developed to bind to and neutralize the actions of both TGF-α and epiregulin. To date 2 recent phase 1 studies have assessed the effects of LY3016859 in both healthy volunteers and DN patients [12]. Although these studies demonstrated that this compound is relatively safe, they were unable to show any significant change in proteinuria, albumin creatinine ratio or renal function when compared to placebo.

Drugs Targeting Oxidative Stress

Nox 1/4 Inhibitors

Oxidative stress is potentially involved in the pathogenesis of DN [1]. NOX enzyme isoforms are involved in the production of reactive oxygen species and the devel-

Table 1. Outcome of recent clinical trials with putative renoprotective agents

Target	Drug	Mechanism	Trial	Outcomes
Vasculature	AKB-9778	Tie2 activator	Phase 2a trial, *n* = 144 AKB-9778 with ranibizumab in patients with diabetic macular oedema	Significant reduction in macular oedema vs ranibizumab monotherapy
	Liraglutide	GLP-1 agonist	LEADER trial, *n* = 9,340 Liraglutide in patients with T2DM and high cardiovascular risk	Significant reduction in secondary composite renal outcomes: new macroalbuminuria, increase serum creatinine, ESRD, death due to renal disease
	Empagliflozin	SGLT2 inhibitor	EMPA-REG OUTCOME trial, *n* = 7,020 Empagliflozin in patients with T2DM and high cardiovascular risk	Significant reduction in secondary composite renal outcomes: incident or worsening nephropathy and incident albuminuria.
Inflammation	CCX140-B	CCR2 antagonist	Phase 2 trial, *n* = 332 CCX140-B alongside RAAS inhibition in patients with T2DM and DN	5mg CCX140-B significantly lowered albuminuria
	NOX-E36	CCL2 antagonist	Phase 2a trial, *n* = 75 NOX-E36 in patients with T2DM and DN	Generally safe and well tolerated Reduction urinary ACR
	Baricitinib	JAK1/2 antagonist	Phase 2 trial, *n* = 129 Baricitinib in T2DM patients at risk of progression to DN	Significant reduction in albuminuria Anaemia main side effect
	Pentoxifylline	Phosphodiesterase inhibitor	PREDIAN trial, *n* = 169 Pentoxifylline and RAAS inhibition in T2DM patients with DN	Smaller decrease in eGFR and significant reduction in albuminuria GI side effects
	LY3016859	Anti-TGF-α/ epiregulin	Phase 1 trials LY3016859 in healthy volunteers (*n* = 56) and T1DM and T2DM patients with DN (*n* = 15 [A] and *n* = 45 [B])	Safe No significant change proteinuria/ ACR or renal function
Oxidative stress	GKT137831	NOX1/4 inhibitor	Phase 2 trial, *n* = 155 GKT137831 in patients with DN	Safe No significant reduction albuminuria
	Allopurinol	Xanthine oxidase inhibitor	Randomised controlled trial, *n* = 176 Allopurinol in patients with T2DM and hyperuricaemia	Reduction serum uric acid, urinary albumin and BP

opment of inflammation and the pathogenic environment [1]. NOX inhibitors have been proposed as a potential therapeutic option. A recent study has shown a beneficial effect of GKT137831, a NOX1/4 inhibitor in murine models of DN [13]. However, a phase 2 trial of GKT137831 in patients with T2DM and albuminuria failed to show any significant renal benefit (https://www.businesswire.com/news/home/20150909005080/en/Genkyotex-Announces-Top-Line-Results-Phase-2-Clinical).

Recently, several studies have investigated the effect of pan-NOX inhibitor APX-115 on DN and shown a clear APX-115-mediated renal benefit in an experimental animal model of diabetes [14]. The results of studies assessing the effects of pan-NOX inhibitors in humans will be of great interest.

Allopurinol

Allopurinol, a xanthine oxidase inhibitor, is a therapy that is currently used to treat hyperuricaemia (e.g., conditions such as gout). Recently, there has been evidence to suggest that xanthine oxidase inhibitor may be beneficial in DN. Many studies have suggested that allopurinol not only lowers levels of uric acid in patients with T2DM and DN but also significantly reduces proteinuria when taken in ad-

dition to RAAS blockade. A recent randomised clinical trial in patients with T2DM and asymptomatic hyperuricaemia demonstrated that treatment with allopurinol over 3 years resulted in significantly reduced serum uric acid, urinary albumin excretion rate and blood pressure [15]. This medication tends to be fairly well tolerated by patients and is readily available; so, it would be a practical addition to current treatment for DN. The PERL trial assessing the effects of allopurinol in patients with T1DM is currently ongoing (ClinicalTrials.gov Identifier: NCT02017171).

Discussion

As briefly discussed, there are several experimental therapies for DN that are currently being tested (Table 1). These include the use of existing medications such as pentoxifylline, allopurinol, SGLT2 inhibitors and GLP-1 agonists, and assessing their application in DN. Further newer medications that are particularly promising include CCL2 and CCR2 inhibitors as well as anti-oxidative stress therapies such as NOX inhibitors. With knowledge of the pathogenesis of DN expanding, new potential therapeutic targets are being discovered. Many of these are still in an early clinical trials stage, but results are promising. It is likely that within the next decade some of these will be available for clinical use; potentially providing new therapeutic options for the many patients who are affected by this devastating diabetic complication.

Disclosure Statement

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