Bioorganic & Medicinal Chemistry Letters 26 (2016) 4394–4402

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Digest paper

Emerging therapeutics for the treatment of diabetic nephropathy

Jehrod Brenneman [a,*], Jon Hill [b], Steve Pullen [c]

[a] Small Molecule Discovery Research, Boehringer-Ingelheim Pharmaceuticals Inc., 900 Ridgebury Rd., Ridgefield, CT 06877, USA
[b] Research Networking, Boehringer-Ingelheim Pharmaceuticals Inc., 900 Ridgebury Rd., Ridgefield, CT 06877, USA
[c] Cardiometabolic Disease Research, Boehringer-Ingelheim Pharmaceuticals Inc., 900 Ridgebury Rd., Ridgefield, CT 06877, USA

ARTICLE INFO

Article history:
Received 28 June 2016
Revised 27 July 2016
Accepted 29 July 2016
Available online 1 August 2016

Keywords:
Kidney disease
Diabetic nephropathy
Fibrosis
Inflammation
Therapeutics

ABSTRACT

Diabetic nephropathy (DN) is the most common pathology contributing to the development of chronic kidney disease (CKD). DN caused by hypertension and unmitigated inflammation in diabetics, renders the kidneys unable to perform normally, and leads to renal fibrosis and organ failure. The increasing global prevalence of DN has been directly attributed to rising incidences of Type II diabetes, and is now the largest non-communicable cause of death worldwide. Despite the high morbidity, successful new treatments for DN are lacking. This review seeks to provide new insight on emerging clinical candidates under investigation for the treatment of DN.

Kidney disease is characterized by abnormal function and/or structural alterations typically arising from inflammation, hemodynamic effects, and genetic predispositions that manifest in fibrotic lesions and eventual irreversible organ damage. Repeated or chronic insult to the kidneys results in irreversible fibrotic damage of the glomeruli (glomerulosclerosis) and kidney tubules (tubulointerstitial fibrosis), and can lead to chronic kidney disease (CKD).[1] CKD is a hallmark of multiple pathological conditions including primarily diabetic nephropathy (DN), focal segmental glomerulosclerosis (FSGS), Berger's syndrome (IgA nephropathy), polycystic kidney disease, and lupus nephritis (LN). If allowed to progress, CKD will eventually transition to end-stage renal disease (ESRD), requiring dialysis or transplant for survival.

CKD is the largest non-communicable cause of death globally, resulting in tens of millions of deaths annualy.[2] It is estimated that CKD affects 8–16% of the worldwide population, and in the US alone is projected to affect nearly 1 in 5 adults by 2050.[3,4] Globally, diabetes is the major cause of CKD, and incidences of Type II diabetes are expected to continue to rise as affluence and the large aging populations in developing nations increase. Despite the increased burden on global healthcare systems, few new drugs to treat kidney disease have been successfully developed over the past 16 years.[5] This may be due to the complexity of etiological factors leading to CKD, a lack of clinical efficacy, or the prevalence of dialysis and kidney transplant interventions as life sustaining measures. Clinical failures may in part be due to the unknown or lack of predictivity of preclinical models of CKD and diabetic nephropathy for efficacy in patients. However, the projected increases in CKD will far outpace the ability of health care systems to provide these costly interventions. This clear need for the development of new therapeutics that curb disease progression to ESRD, in conjunction with improved early diagnostic capabilities, has led to the development of a clinical pipeline of new therapeutics to address the unmet global medical need. Although, no drugs have demonstrated efficacy in recent Phase III trials despite robust responses in preclinical studies and encouraging Phase II results, the increasing clinical activity in CKD provides hope that new therapies will be developed. While the subject of new drugs for CKD has been reviewed, this Letter will focus on emerging therapeutic concepts positioned specifically for the treatment of DN.[6–17] It will also be limited in its discussion of drugs being repurposed for DN from other disease indications.

Historically, the treatment of DN has relied on tackling the broad cardiovascular and diabetic factors (primarily blood pressure and blood glucose levels) that are inextricably linked to renal disease, rather than focused therapeutics targeting kidney inflammation and fibrotic processes. This is in part due to the shared pathways of tissue injury between cardiovascular disease, diabetes, and DN, but is also a result of the success obtained in managing progression of DN to ESRD with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) that interfere with the renin-angiotensin system (RAS). Blockade of this system has proven beneficial in clinical trials of

* Corresponding author. Tel.: +1 203 778 7961; fax: +1 203 798 5297.
E-mail address: jehrod.brenneman@boehringer-ingelheim.com (J. Brenneman).

http://dx.doi.org/10.1016/j.bmcl.2016.07.079
0960-894X/

diabetic kidney disease in reducing proteinuria and providing renal protection beyond just blood pressure control and has led to their adoption as current pharmaceutical standards of care.[18–22] Even with these treatments, progression of renal disease to ESRD still occurs in approximately 20% of patients with kidney disease due to diabetes.[23]

Beyond RAS blockade, a number of potential therapies have emerged in recent years to treat CKD and the many sub-pathologies that contribute to CKD progression and DN specifically. These include drugs that primarily target pro-inflammatory and innate immune responses that drive pathogenesis in FSGS, IgA nephropathy, and LN, but also drugs that target oxidative stress and pro-fibrotic tissue remodeling programs characteristic of ischemic injury and DN (Fig. 1). In this review, the potential therapeutics have been classified and divided either as new investigational entities undergoing clinical evaluation or as currently-marketed drugs that are being repositioned to treat DN. The therapeutics presented in this review were identified according to the criteria listed in Figure 2.

Launched therapeutics under investigation for DN: As a better understanding of the mechanistic drivers of disease progression in CKD has begun to unfold, new applications for established therapeutics that impact those factors are being recognized. In recent years, many launched drugs for other indications have been repositioned to treat CKD and DN specifically. These drugs include antihypertensives and molecules that combat oxidative stress. The majority of these drugs are indicated for cardiovascular diseases such as pulmonary arterial hypertension (PAH) or for controlling disorders associated with proliferation of reactive oxygen species (ROS). A synopsis of the approved drugs under investigation in DN is provided in Table 1. Discussion of these drugs will be limited to specific instances in which an emerging investigational therapeutic shares the same primary mechanism of action. Additional trials that were terminated or completed in previous years but are pending release of outcome data in DN or related renal diseases are included for reference.

Promising new therapeutics: A number of new unlaunched therapeutics have advanced into clinical trials over the past 5 years for DN. While several reviews have highlighted some of these new molecular entities as recently as 2015, substantial rates of attrition have been observed due to a failure to meet primary clinical endpoints or from strategic shifts in company portfolios. Table 2 captures promising investigational drugs still under active clinical development for DN as of April 2016.

GPCR targeting approaches: Endothelin-1 receptor A antagonists: Endothelin-1 is pleiotropic peptide that activates both endothelin receptor subtypes A and B and has been shown to contribute to renal impairment in patients with CKD.[24–27] Activation of endothelin-1 receptor A (ER_A) in the kidney results in increased oxidative stress, vasoconstriction, podocyte injury, inflammation, and fibrosis, whereas ER_B activation is anti-proliferative, anti-fibrotic, natriuretic, and vasodilatory.[27] In this light, the often-modest (<1000-fold) selectivity for ER_A over ER_B is hypothesized to be a major contributor to adverse CV effects, anemia, and edema observed clinically for early ER_A antagonists, thereby precluding their application in CKD. More selective antagonists have emerged in recent years, and are now positioned for evaluation in DN trials.

Atrasentan (ER_A:ER_B selectivity 1860:1)[28] is currently under investigation in the Ph III SONAR trial of 4148 patients for DN, with an expected completion date of 2018.[29] The ability of atrasentan to delay the progression to ESRD, doubling of serum creatinine (SCr), or death will serve as the primary composite endpoint. Patients at risk of peripheral edema have been excluded from this trial on the basis of previous findings in Ph II studies with higher doses of the inhibitor.[7] Atrasentan also lacks the recurring aryl sulfonamide motifs of previous ER_A antagonists, which may provide a reduced risk of hepatotoxicity. It should be noted that sparsentan, a dual-acting receptor antagonist (DARA) that combines the core of the

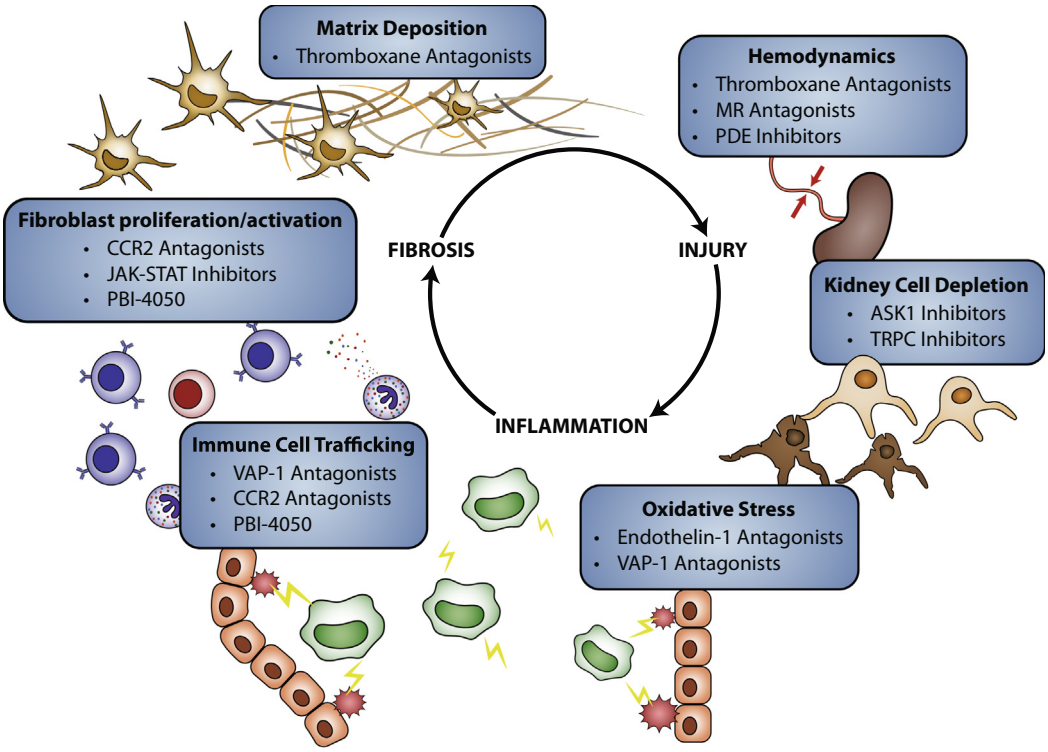

Figure 1. Pathogenic processes in DN and potential targeting strategies under clinical investigation.