Drug therapies to delay the progression of chronic kidney disease

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Chronic kidney disease (CKD) is associated with significant morbidity and mortality, impacted not alone by progression to end-stage kidney disease, but also by the high associated incidence of cardiovascular events and related mortality. Despite our current understanding of the pathogenesis of CKD and the treatments available, the reported incidence of CKD continues to rise worldwide, and is often referred to as the silent public healthcare epidemic. The significant cost to patient wellbeing and to the economy of managing the later stages of CKD have prompted efforts to develop interventions to delay the development and progression of this syndrome. In this article, we review established and novel agents that may aid in delaying the progression of CKD and improve patient outcomes.

KEYWORDS: Chronic kidney disease, progression, drug therapy

Introduction

Chronic kidney disease (CKD), as defined by proteinuria or a reduced glomerular filtration rate (GFR) below 90 mL/min/1.73 m² persisting for greater than 3 months, is reported to affect 13% of US adults. There is a significantly higher prevalence in the elderly and those with hypertension or diabetes, and with these comorbidities increasing in prevalence and the population ageing, CKD is projected to affect up to 16% of adults by 2030. Even in its early stages, CKD is associated with accelerated cardiovascular disease and increased mortality, with an exponential increase in attributable risk as GFR declines to end-stage kidney disease (ESKD). The mortality rate in ESKD patients maintained on dialysis is striking, with a life expectancy less than one-third that of their counterparts without ESKD, and a 5-year survival rate on dialysis of only 40%. There is also a substantial healthcare cost associated with provision of ESKD care, currently estimated at $33 billion annually in the US, equating to 6.3% of the Medicare Budget. Hence, there may be significant healthcare and economic benefits to be garnered from halting or delaying CKD progression. In this article, we discuss recent evidence for established and emerging therapies that may alter the progression of CKD.

Non disease-specific drug therapies

Sodium bicarbonate

CKD is associated with a metabolic acidosis, particularly at lower levels of GFR <25 mL/min/1.73 m², which is predominantly attributed to reduced hydrogen ion excretion as titratable acids or ammonium in the urine. Chronic metabolic acidosis exacerbates CKD-related mineral bone disease, leads to muscle atrophy, and is associated with other complications such as abnormal albumin synthesis, thyroid dysfunction and insulin resistance. Observational data demonstrate a strong risk of progression of CKD in those with a lower serum bicarbonate level, as well as an increased mortality risk. Possible mechanisms for the deleterious effect of acidosis on GFR may be the inadvertent pro-fibrotic effects of inducing regulatory mechanisms in the kidney, such as increased renal ammonium production, endothelin-A receptor activation and prolonged activation of the renin–angiotensin system. A systematic review of six randomised controlled trials which administered oral sodium bicarbonate to pre-dialysis CKD patients, versus standard of care treatment or placebo, demonstrated a net improvement in GFR with alkali therapy, as well as reduced initiation of renal replacement and no safety concerns in the longer term. Hence, this appears to be a safe and inexpensive therapy to delay progression of CKD.

Erythropoiesis-stimulating agents and iron therapy

Anaemia and iron deficiency are twice as common in CKD patients compared to the general population, with up to 60% of later stage CKD patients affected. Iron deficiency in this population is attributable to poor dietary intake, iron malabsorption or occult blood loss, or the phenomenon of a functional iron deficiency associated with an inflammatory state. General investigations should exclude other causes of anaemia. Severe anaemia in CKD is linked to increased cardiovascular events and hospitalisation, inferior survival and increased progression to ESKD. The introduction of erythropoiesis-stimulating agent (ESA) therapy has greatly
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Reduced reliance on blood products for correction of severe anaemia associated with CKD. However, unlike correction of severe anaemia (Hb <9 g/dL), correction of mild or moderate haemoglobin levels in CKD has not been shown to improve cardiovascular outcomes.22–24 Furthermore, correction to conventionally ‘normal’ haemoglobin levels by ESAs compared to more modest targets in CKD patients, particularly with rapid correction or a requirement for high-dose ESAs, is linked to increased risk of cardiovascular events and mortality without an incremental measured benefit.22–24 There is also no evidence that ESA use influences the rate of progression of CKD at any stage.22

There has been increased interest in non-ESA anaemia therapies in particular CKD cohorts. There is a growing recognition of the high prevalence of iron deficiency in chronic heart failure (CHF) patients, and the benefit of iron administration in terms of myocardial function and cardiac clinical endpoints.25–27 The presence of ischaemic CKD in the presence of CHF, so called cardiorenal syndrome, is also an increasingly encountered clinical entity. Administration of iron to iron-deficient cardiorenal syndrome patients has recently been shown to improve their renal function.28 Comparison of oral versus intravenous iron administration across the spectrum of CKD aetiologies currently favours the intravenous route in terms of iron repletion efficacy and reduction in reliance on ESAs, with a good reported safety profile.29,30 Clinical guidelines suggest haemoglobin levels should not be maintained above 11.5 g/dL by ESA therapy, and that selection of the route of iron administration should be based on severity of the anaemia and iron deficiency, prior response or intolerance to treatments, availability of venous access, cost implications and current ESA use.31

Urate-lowering therapy

Hyperuricemia, even in the absence of symptomatic urate crystal deposition, is an independent risk factor for mortality, cardiovascular disease, hypertension and CKD in the general population. Hyperuricemia is highly prevalent in CKD due to reduced renal excretion of uric acid as the GFR declines. Observational data suggest that high serum uric acid levels in CKD patients are associated with an increased all-cause and cardiovascular mortality, and may also contribute to CKD progression.32–34 However, it remains unclear whether hyperuricemia is a mediator or confounder in the CKD–cardiovascular disease–mortality axis. Lowering of serum uric acid with the xanthine oxidase inhibitor allopurinol has been observed to significantly improve hypertension, mortality and estimated GFR in patients with hyperuricemia in the general population.35,36 In a small group of CKD patients with GFR <60 mL/min, administration of allopurinol 100 mg daily over a 24-month period was associated with a relative preservation of renal function, reduced cardiovascular events and reduced hospitalisations compared to placebo.37 The novel agent febuxostat had an enhanced effect compared to allopurinol in a small retrospective cohort study of hyperuricemic CKD patients.38 However, two recent meta-analysis and systematic review studies of allopurinol use in CKD patients did not demonstrate clear evidence of retarding progression of CKD or reducing cardiovascular events, although therapy appears to be safe.39–40 Current clinical guidelines are ambivalent regarding the benefit of urate-lowering therapy in CKD and do not specifically recommend this strategy at present.41

Renin–angiotensin system inhibition

Angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), and perhaps direct renin inhibitors, are standard of care treatment in proteinuric CKD, with a role in delaying progression of CKD compared to other anti-hypertensive medications, although unfortunately the risk of CKD progression still remains high.42–44 The antihypertensive, antiproteinuric and renal protective effects among different ACEi and ARBs drugs, as well as between classes, are generally thought to be equivalent. While many reports have highlighted the enhanced anti-proteinuric and renal protective effect when combining ACEi and ARBs, so called ‘dual renin–angiotensin system (RAS) blockade’ strategy, there is now a growing body of literature to caution against this practice.45,46

The ONTARGET trial of telmisartan alone versus combined ramipril and telmisartan in patients with established atherosclerotic vascular disease or diabetes with end-organ damage was the first major trial to cast doubt on the benefit of dual RAS blockade, demonstrating similar nephroprotective effects to monotherapy but significantly higher adverse event rates with dual therapy, despite a significant lowering of proteinuria.47 A recent meta-analysis of dual RAS inhibitor therapy in CKD patients demonstrated a higher risk of hypotension, hyperkalaemia and net GFR decrease, without mortality benefit, compared to monotherapy.48 A systematic review of randomised controlled trials of dual RAS inhibition in patients with albuminuria and cardiovascular risk factors similarly did not demonstrate any reduction in progression to ESKD or mortality compared to monotherapy with an ACEi or ARB.49 A further recent meta-analysis, not specifically focusing on a CKD population, again reported no mortality benefit associated with dual blockade over monotherapy, regardless of heart failure status, with higher rates of renal adverse effects and treatment withdrawal in dual blockade cohorts.50 The ALITITUDE and NEPHRON D studies, which both investigated dual RAS blockade in diabetic CKD patients, were terminated prematurely due to safety concerns including adverse renal outcomes.51,52 Of note, in the latter study, there was a significant trend towards clinical benefit that potentially supported the use of dual blockade, with a 34% risk reduction of the primary endpoint of death, ESKD or predefined reductions in GFR at the time of study termination. Indeed, some experts continue to believe that there may be a role for dual RAS blockade, with appropriate patient selection and close monitoring and titration of agents, but this remains to be proven. The ongoing VALID trial is investigating whether use of halved doses of agents in a dual RAS blockade regimen can prove superiority to monotherapy without the associated adverse events. The European Medicines Agency are also conducting a review into the combined use of RAS blocking agents.49

Mineralocorticoid receptor antagonists

A recent Cochrane review of aldosterone receptor antagonist use in 1,549 mild to moderate CKD patients in 27 clinical

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trials demonstrated a significant reduction in proteinuria and blood pressure in these patients, in addition to that achieved with either single or dual-agent RAS inhibition, with an increased risk of hyperkalaemia and gynaecomastia.\(^5^4\) There was insufficient evidence to comment on any clear beneficial effect in terms of preservation of renal function or reduction in cardiovascular events in CKD patients. The RALES trial demonstrated a significant survival benefit for spironolactone use in heart failure patients with reduced ejection fraction, with CKD patients included if the serum creatinine level was below 221 µmol/L at randomisation.\(^5^5\) Two ongoing randomised, controlled clinical trials, the BARACK-D and STOP-CKD trials, will report on whether the addition of spironolactone to standard of care management in mild to moderate CKD can safely reduce cardiovascular events and mortality, with the effects on GFR to be reported as secondary outcomes.\(^5^6,5^7\)

Statin therapy

CKD is considered a major risk factor for cardiovascular disease, and statin therapy is indicated to reduce cardiovascular events in pre-dialysis CKD patients based on a number of randomised controlled trials. These include the SHARP trial which, in addition to finding a significant reduction in atherosclerotic event with simvastatin and ezetimibe in CKD, demonstrated no impact of statin use on progression of CKD.\(^5^8\) A subsequent systematic review of 38 prospective, controlled, randomised trials of statin use in patients with non-dialysis dependent CKD showed no clear benefit of statin use in terms of delaying or halting progression to ESKD, while consistently lowering mortality and major cardiovascular events by 20%.\(^5^9\)

Obesity

Obesity is a common contributing factor to the development of CKD, leading to predisposing risks such as diabetes, hypertensive nephrosclerosis, renal stone formation and hyperfiltration injury. Obese patients appear to particularly benefit from RAS inhibition in terms of its anti-proteinuric effect.\(^6^0\) In CKD patients, a BMI >35 kg/m\(^2\) is associated with worse survival in patients with early stage CKD, but this finding is attenuated in those with a GFR <30 mL/min.\(^6^1\) Conversely, it is interesting that observational evidence in dialysis patients suggest that a high body mass index (BMI) is associated with better survival in ESKD. Non-pharmacological intervention with bariatric surgery in morbidly obese CKD patients can lead to an improvement in GFR, blood pressure control and proteinuria, but longer term studies with the clinical endpoint of preservation of GFR to be reported as secondary outcomes.\(^6^2,6^3\)

Vitamin D

Vitamin D deficiency has been associated with cancer, heart disease, and stroke in a cohort of over 25,000 patients with DN demonstrated an improvement in GFR at one year and a reduction in progression to ESKD associated with pirfenidone use, although the study population was small.\(^7^0\) Another randomised, placebo-controlled trial of use of two dose regimes of pirfenidone in young CKD stages 1–4 patients of varying aetiology has been completed and results are awaited (NCT00001959).

Pirfenidone

The anti-fibrotic drug pirfenidone, which blocks transforming growth factor-β, had beneficial effects on GFR preservation in animal studies. A small clinical trial involving patients with chronic focal and segmental glomerulosclerosis demonstrated preservation of GFR associated with pirfenidone, although there was no placebo control and some concerns about the GFR calculation methodology employed.\(^6^9\) A subsequent placebo-controlled, randomised, double-blinded study in patients with DN demonstrated an improvement in GFR at one year and a reduction in progression to ESKD associated with pirfenidone use, although the study population was small.\(^7^0\) Anti-fibrotic and anti-inflammatory targeted therapies

Pentoxifylline

CKD is an inflammatory state, with higher circulating inflammatory markers than the general population. Early studies suggested that pentoxifylline, a methylxanthine phosphodiesterase inhibitor with favourable anti-inflammatory effects and immune-regulatory properties, may be beneficial in this setting. A systematic review and meta-analysis showed pentoxifylline had an enhanced anti-proteinuric effect, in combination with RAS inhibition, and was associated with some improvement in renal function without significant adverse effects.\(^6^7,6^8\) However, the supportive data are methodologically flawed, of short follow-up duration and in small sample sizes. There is insufficient evidence at present to recommend its widespread use. A phase II, randomised, double-blinded, placebo-controlled study to evaluate the safety and efficacy of CTP-499, an active metabolite of pentoxifylline, is now complete in type-2 diabetic nephropathy (DN) patients also treated with RAS inhibition and results are awaited (NCT01847109).

Endothelin receptor antagonists

Endothelin-1 is almost universally increased in kidney disease. This may exert a pathological effect in CKD via increased risk of hyperkalaemia and gynaecomastia.\(^5^4\) There was insufficient evidence to comment on any clear beneficial effect in terms of preservation of renal function or reduction in cardiovascular events in CKD patients. The RALES trial demonstrated a significant survival benefit for spironolactone use in heart failure patients with reduced ejection fraction, with CKD patients included if the serum creatinine level was below 221 µmol/L at randomisation.\(^5^5\) Two ongoing randomised, controlled clinical trials, the BARACK-D and STOP-CKD trials, will report on whether the addition of spironolactone to standard of care management in mild to moderate CKD can safely reduce cardiovascular events and mortality, with the effects on GFR to be reported as secondary outcomes.\(^5^6,5^7\)

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vasoconstriction, proteinuria, inflammation, cellular injury and ultimately fibrosis mediated by stimulation of the endothelin-A (ETA) receptor subtype. Activation of ETA receptors in vascular smooth muscle causes potent vasoconstriction, while activation of endothelin-B (ETB) receptors induces vasodilatation via nitric oxide and prostaglandin release. ETB receptors also reduce arterial pressure by promoting natriuresis and diuresis through direct inhibition of nephron sodium and water reabsorption. The ETA receptor antagonist, avosentan, has demonstrated significant additional anti-proteinuric effects added to RAS inhibition in patients with DN, but treatment was associated with dose-dependent fluid retention. The ASCEND trial examined the effect of avosentan on progression of renal disease or death in type-2 DN patients on RAS blockade. Again, avosentan reduced proteinuria, but the trial was terminated early due to serious adverse cardiovascular events, including a three-fold increased risk of congestive cardiac failure. The early due to an increased cardiovascular event rate, which may have been mediated by modulation of endothelin activity, with a resultant sodium and fluid retention, whereas lower doses may have been effective to block ETA receptors more selectively. Currently, a large, multinational, double-blind, placebo-controlled phase-III clinical study of the use of atrasentan in patients with DN (SONAR) is recruiting. Atrasentan is a highly selective ETA receptor antagonist, which showed a similar adverse event profile in phase-II studies compared to placebo. With appropriate patient selection, particularly avoiding those with advanced CKD or known congestive heart failure, careful dosing regimens and escalating diuretic use when required, there may be an important role for this class of agents in the treatment of CKD.

Bardoxolone
In the BEACON trial, the antioxidant bardoxolone (compared to placebo) did not reduce the risk of death or progression to ESKD in stage 4 CKD patients; the trial was terminated early due to an increased cardiovascular event rate, which may have been mediated by modulation of endothelin activity, with a resultant sodium and fluid retention. The enteric uraemic toxin adsorbent AST-120 was reported in surgery patients at high risk of developing acute kidney injury, demonstrating regenerative properties, and in a recent phase-I trial in cardiac surgery patients at high risk of developing acute kidney injury, MSC administration was feasible and safe. A systematic review and meta-analysis of 71 preclinical trials demonstrated that cell-based therapy reduced the development and progression of CKD. Prominent results were noted for urinary protein (standardised mean difference (SMD), 1.34; 95% confidence interval (CI), 1.00–1.68) and urea (SMD, 1.09; 95% CI, 0.66–1.51), with both significantly improved (p<0.001). Changes in plasma urea were associated with changes in both glomerulosclerosis and interstitial fibrosis. The timing of therapy in relation to clinical manifestation of disease, and cell origin and dose, were not associated with efficacy.

Diabetic nephropathy
Traditional risk factor management
DN affects 20–30% of diabetic patients and is a leading cause of ESKD, as well as being strongly associated with cardiovascular morbidity and mortality. Traditional management involves blood pressure control, glycaemic control and RAS inhibition. The ACCORD trial series evaluated the benefit of more intensive management in type-2 diabetes patients with two or more cardiovascular risks, with the primary endpoint of combined non-fatal or fatal major cardiovascular event, with some trials also reporting renal outcomes. Intensive glycaemic control (HbA1c <6.0 vs 7.0–7.9%) increased mortality with no reduction in major cardiovascular events. With the exception of a significant 29% lower incidence of established proteinuria during the trial, all renal microvascular outcomes, including progression to ESKD, were similar in the intensively managed and standard groups in the subsequent follow-up study. A Cochrane systematic review of over 20,000 type-2 diabetes patients demonstrated the benefits of intensive glycaemic control in terms of microvascular outcomes, including a 25% risk reduction for developing nephropathy, but interestingly did not find the previously associated increased mortality risk. A systematic review of 12 major trials in type-1 diabetes patients showed that intensive glycaemic control was associated with a significant 44% risk reduction of developing nephropathy, although rates of progression to ESKD were similar once the nephropathy was manifest. Most data involved younger patients without overt macrovascular complications, and so the benefit of intensive glycaemic control in older type-

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1 diabetic patients with established cardiovascular disease remains unclear. ACCORD also demonstrated that lowering systolic blood pressure to <120 mmHg compared to a target <140 mmHg in those with good glycaemic control did not improve cardiovascular outcomes. It was, however, associated with increase rates of adverse events such as hyperkalaemia and episodes of acute kidney injury. There was a reduction in incident proteinuria at the end of the trial, but no beneficial effect on progression to ESKD or need for dialysis.

Addition of fenofibrate (vs placebo) to simvastatin in the ACCORD cohort was associated with elevation in serum creatinine after initiation of the drug, which then remained constant. Again a reduced incidence of proteinuria was reported, but no impact on progression to ESKD or need for dialysis.

Novel oral hypoglycaemic agents

Novel oral hypoglycaemic agents may hold some promise in the management of DN. Dipeptidyl peptidase IV (DPP-IV) inhibitors enhance insulin secretion and reduce glucagon secretion by inhibiting the degradation of glucagon-like peptide-1. Various agents are available, although linagliptin, which is primarily eliminated by the liver and requires no dose adjustment in CKD, appears to be an attractive agent for use in patients with DN. A meta-analysis of 13 randomised controlled trials involving over 5,500 patients demonstrated that use of linagliptin caused a 16% reduction in a composite renal end point consisting of micro- or macro-albuminuria, loss of eGFR >50% from baseline, acute renal failure or death.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, such as empagliflozin and canagliflozin, have proven efficacy in improving glycaemic control with the added benefit of weight loss by inhibiting proximal tubular glucose reabsorption. Diabetic animal model studies have shown the positive effect of these agents on renal hyperfiltration, with reduction in both proteinuria and histological changes of nephropathy. The ATIRMA trial studied the effects of once daily empagliflozin in 42 type-1 diabetic patients with and without hyperfiltration. It demonstrated a significant 20% reduction in hyperfiltration along with improved glycaemic and blood pressure control and reduction in insulin requirements. The SGLT2 inhibitors appear safe and there are no notable interactions with RAS-blocking agents to date. The efficacy of these agents will diminish as GFR declines, as the rate of urinary glucose excretion and the amount of glucose available for SGLT2 inhibition depend on the amount of glucose filtered in the glomerulus. Hence, the role of these agents in long-term renal protection may require that they be initiated early before there has been a significant decline in GFR with established DN. Further prospective trials will be required to examine the role and optimal timing of use for these agents in primary and secondary prevention of DN, with larger trials testing effectiveness in improving clinical renal and cardiovascular outcomes.

Polycystic kidney disease

mTOR inhibition

Autosomal dominant polycystic kidney disease (ADPKD), caused by mutations in genes polycystin-1 or polycystin-2, typically presents with progressive renal failure from the fourth decade, with a rate of GFR decline in the order of 4-6 mL/min per year. It is the most common inherited genetic cause for ESKD. There has been significant interest in attempting to find pharmacological interventions to retard cyst growth and disease progression. The SIRENA randomised cross-over trial suggested a benefit of mTOR inhibitors retardation of cyst growth and renal failure with tolvaptan V2 receptor antagonists, such as tolvaptan. PKD rodents lacking circulating vasopressin appear to be protected from cyst formation, until exogenous vasopressin is introduced and cyst growth ensues. A landmark randomised control trial in patients with ADPKD (TEMPO 3:4) reported lower rates of kidney growth and significant kidney function preservation with tolvaptan compared to placebo, albeit with higher rates of drug intolerance and discontinuation in the intervention arm.

It is notable that patients in both arms were advised to maintain a high fluid intake, which will as a consequence inhibit vasopressin activity, and could potentially have blunted any additional therapeutic benefit of tolvaptan administration. Extension studies are ongoing, and tolvaptan has been provisionally approved for use in ADPKD by the European Medicines Agency, having been previously licensed for this indication in Japan in 2014. The US Food and Drug Administration have declined to license the drug to date over concerns of hepatotoxicity and lack of supporting trials, which, when combined with significant cost implications, has led to reluctance in accepting it into widespread clinical practice at this juncture.

Conclusion

CKD is a common condition that leads to increased cardiovascular morbidity and mortality, as well as progression to ESKD. Many of the current treatments for CKD focus on cardiovascular risk modification, and there are a number of safe and cost-effective therapies that slow the progression of CKD. Unfortunately, despite such measures, the incidence of CKD continues to rise, therapy retards rather than halts progression to ESKD, and the burden of adverse outcomes caused by CKD remains high. New agents to prevent CKD progression and reduce cardiovascular morbidity in this growing patient population are urgently needed.
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Faints, fits and funny turns for the physician

Author: Rohani Omar

The diagnosis and management of the dizzy patient presents the physician with significant challenges. Dizziness and imbalance are common complaints among the general population, affecting around one-third of people over the age of 65 years, and can result from a range of causes spanning many medical disciplines. The ability to take a thorough, accurate history with a logical framework for formulating a differential diagnosis is essential given the many ways that symptoms of dizziness can present. An understanding of the key features of the vestibular examination, and consideration of other pathologies including neurological and cardiac, are important. This conference was held with the aim of demystifying the dizzy patient by providing physicians with a practical approach to the assessment and management of dizziness, imbalance and ‘funny turns’.

KEYWORDS: Dizziness, imbalance, vestibular, vertigo, syncpe, seizures

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Introduction

There can be few physicians so dedicated to their art that they do not experience a slight decline in spirits when they learn that their patient’s complaint is dizziness.1

Presentations of dizziness, imbalance, blackouts and ‘funny turns’ are common, yet many physicians struggle with the diagnosis and management of these symptoms. On 30 April 2015, a conference was organised by the Royal College of Physicians with the aim of providing a clinically focused, practical approach to the management of this challenging patient population. Key features of history taking, clinical examination and formulating a differential diagnosis of common conditions were covered. Case studies were used to illustrate different conditions and allow for audience participation in the form of anonymous voting using response pads to answer questions.

Epidemiology and principles of management

Vertigo of a vestibular cause is common, affecting more than 5% of adults per year. Around one-third of people over the age of 65 years living in the community report symptoms of