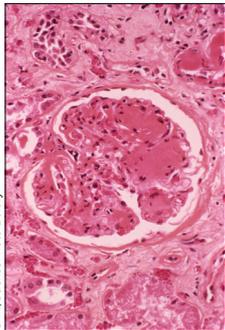


CCR2 inhibition: a panacea for diabetic kidney disease?



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Diabetic nephropathy is associated with high cardiovascular morbidity and mortality and reduced quality of life. Drugs such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB), which modify the activity of the renin angiotensin system (RAS), might provide up to a 20% relative risk reduction benefit for slowing the progression of established kidney disease.^{1,2} Information about how to prevent progression of early diabetic kidney disease with these drugs is scarce. Results of short-term studies have shown the ability of RAS blockers to prevent progression from normoalbuminuria to microalbuminuria,³ from microalbuminuria to macroalbuminuria,⁴ and from macroalbuminuria to doubling of creatinine concentration, end-stage renal disease, or death.^{1,2} Findings from several clinical trials and a meta-analysis⁵ have shown that the reduction of albuminuria is associated with a reduction in progression of diabetic kidney disease. However, there are no prospective clinical trials linking suppression of albuminuria with delay in progression of diabetic kidney disease so far.

Nevertheless, a reduction in albuminuria might serve as a biomeasure of therapeutic success, especially with RAS blockers. Clinical trials have been done to assess strategies to amplify the antiproteinuric effects of RAS blockers. Therapeutic opportunities that have some evidence of benefit include greater blood pressure reduction, limitation of dietary salt intake, and the use of concurrent thiazide diuretic treatment.⁶ Use of increased doses of RAS inhibitors or two different types of RAS inhibitors resulted in small reductions in albuminuria, but were associated with adverse events that have restricted the use of such approaches in clinical practice.⁷

Why does diabetic nephropathy progress so relentlessly in patients in the presence or absence of albuminuria? This is a crucial question because it delves into the mechanism of disease, and specific strategies to change glomerular haemodynamics with RAS blockers and suppress inflammation through different anti-inflammatory strategies. One such strategy was investigated in a clinical trial by Dick de Zeeuw and colleagues,⁸ reported in *The Lancet Diabetes & Endocrinology*. In a multicentre, double-blind, placebo-controlled trial in 332 patients with type 2 diabetes and proteinuria, the investigators assessed whether

CCX140-B, a selective inhibitor CCR2, could further reduce albuminuria when given in addition to standard care, including ACE inhibitors or ARBs. Their results showed that CCX140-B had renoprotective effects on top of current standard of care, based on the primary efficacy outcome of change in urinary albumin to creatinine ratio after 52 weeks (–2% [95% CI –11% to 9%] for placebo vs –18% [–26% to –8%] for 5 mg CCX140-B and –11% [–20% to –1%] for 10 mg CCX140-B).

The suppression of inflammation as a strategy to slow diabetic kidney disease is of major interest to the pharmaceutical industry. CCR2 inhibitors, JAK2 inhibitors, endothelin receptor antagonists, pentoxifylline, and other anti-inflammatory drugs are being studied. Will the effects of these anti-inflammatory drugs incrementally protect kidney function on top of established doses of RAS blockers that target glomerular capillary hypertension? And can this potential effect be adequately measured by change in albuminuria?

de Zeeuw and colleagues' study provides an important opportunity to examine a CCR2 inhibitor in a double-blind prospective clinical trial. Importantly, in this study the average blood pressure was about 137/78 mm Hg, renal function was fairly well preserved, and the urine albumin to creatinine ratio was about 400 mg/g—ie, patients had early stage diabetic kidney disease. A 5 mg dose of the CCR2 inhibitor produced a significant 16% reduction in proteinuria on top of optimum use of RAS inhibition. This effect also persisted for 4 weeks after the drug was stopped, which might suggest that the treatment has a non-haemodynamic effect.

However, many questions remain. First, would the effect be the same in patients with lower blood pressure? In de Zeeuw and colleagues' study, individuals with lower than 130 mmHg systolic blood pressures had less of an antiproteinuric effect with this drug. Likewise, there was very little use of thiazide diuretic in the study (16%). Might the employment of thiazide diuretics with full-dose RAS inhibition coupled with reduced salt intake and a systolic blood pressure of 120 mm Hg completely obviate the need for this newer treatment to facilitate reduction in proteinuria? In the real world, this type of optimum antiproteinuric strategy might not be a realistic opportunity. Alternatively, a CCR2 inhibitor might have the same antiproteinuric effect without the

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need for a reduction in salt intake reduction or diuretic treatment.

This study is an important step in the right direction and the investigators emphasise the need for further exploration of the effects of the CCR2 inhibitor on long-term renal function, presuming that a reduction of proteinuria does serve as an adequate biomeasure of clinical benefit. However, more clinical information is needed—eg, for identification of demographic variables or patient characteristics that can be used to predict response to CCR2 inhibition.

The availability of new oral hypoglycaemic drugs should also be taken into account. Both GLP-1 agonists and SGLT2 inhibitors have antihypertensive and antialbuminuric effects. The oral hypoglycaemics used in the study by de Zeeuw and colleagues were mainly metformin and sulfonylureas. It is therefore unclear whether newer anti-inflammatory treatments such as CCR2 inhibition would be needed if a GLP-1 agonist or an SGLT2 inhibitor was being used in place of these drugs.

Overall, de Zeeuw and colleagues' findings are encouraging and point to a potential new strategy to delay progression of diabetic kidney disease. However, many questions remain about the mechanism of progression of diabetic kidney disease, even in the absence of albuminuria. Ultimately, however, new treatments such as CCR2 inhibitors might provide an opportunity to improve on the 20% relative risk reduction benefit seen in clinical trials with ACE inhibitors and ARBs.

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Cardiovascular safety of albiglutide and other glucagon-like peptide-1 receptor agonists

Since 2008, the US Food and Drug Administration (FDA) has required that any new diabetes drug must be shown to cause no substantial increase in cardiovascular risk, either by a meta-analysis of phase 2–3 trials or in a dedicated prospective cardiovascular outcome trial showing non-inferiority of the drug versus placebo. As a result, numerous meta-analyses have been published and several prospective cardiovascular outcome trials have been planned.^{1,2} Results of some such clinical trials of dipeptidyl peptidase 4 inhibitors have been already

reported, and most of the others are still ongoing and relate to inhibitors of sodium-glucose cotransporter type 2 (SGLT2) or glucagon-like peptide-1 (GLP-1) receptor agonists.¹

GLP-1 receptor agonists are increasingly used for the management of hyperglycaemia in type 2 diabetes. Besides their potent glucose-lowering activity (without inducing hypoglycaemia), they offer the potential of reducing bodyweight, lowering blood pressure (but at the cost of a slight increase in heart rate), and improving some other cardiovascular risk factors.^{3,4} Most of the

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