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Review Article

Advances in the management of chronic kidney disease – a South African perspective

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ABSTRACT

Chronic kidney disease (CKD) represents a significant public health problem globally, and there is evidence to suggest that the prevalence of CKD in sub-Saharan Africa is comparable to elsewhere. For many South African patients who progress to kidney failure (KF), life-sustaining kidney replacement therapy (KRT) is inaccessible due to strict rationing in a resource-limited public healthcare sector, upon which most South Africans are reliant. This shortage brings into focus the need for strategies for delaying CKD progression. This review aims to highlight significant developments in the management of CKD over the last few decades and to discuss these advances within a South African context. That is, to consider the profile of kidney disease locally and issues surrounding access to newer therapeutic agents. We summarise the mechanisms by which the newer therapeutic agents confer renal protection and the major trials supporting their efficacy. Notable advances include newer anti-diabetic agents such as sodium-glucose-transporter-2 (SGLT-2) inhibitors, endothelin-receptor antagonists (ERAs), and nonsteroidal mineralocorticoid antagonists (MRAs). In addition, experimental, targeted therapies in the setting of various glomerular diseases, polycystic kidney disease and APOL-1-mediated kidney disease are briefly discussed. We also highlight several locally relevant advances pertinent to patients on KRT, including newer therapies for managing anaemia in CKD and local experiences with ABO-incompatible kidney transplantation. Although many newer therapies for managing CKD have robust data supporting their use, many barriers exist to implementing them into daily clinical practice.

Key messages

- Although there is a significant burden of CKD in South Africa, many patients are unable to access life-sustaining kidney replacement therapy (KRT) due to the strict rationing of dialysis in a resource-limited public healthcare sector.
- Newer therapies such as sodium-glucose-transporter-2 (SGLT-2) inhibitors, non-steroidal mineralocorticoid receptor antagonists (MRAs) and endothelin receptor antagonists (ERAs) delay the progression of CKD, which is crucial in patients with CKD who may not be able to access KRT.
- It is therefore paramount that we address the barriers limiting access to these newer therapies.

INTRODUCTION

There is a growing burden of chronic kidney disease (CKD) globally, with approximately 1 in 10 adults affected.(1) Many low-to-middle income countries (LMICs) are facing a disproportionate rise in CKD, linked to increases in non-communicable diseases (NCDs), such as hypertension and diabetes mellitus, and exacerbated by high rates of infectious diseases, trauma, pregnancy-related disorders and toxin-induced kidney injury.(2) The true prevalence of CKD in Africa is unknown, with estimates ranging from 4.6% to 10.1%.(3,4) In sub-Saharan Africa (sSA), CKD prevalence has been estimated at 13.9%.(3,5) South Africa is classified as an upper-middle income country (UMIC) with high levels of inequality and faces a "quadruple burden of disease", which drives an epidemic of CKD.(6) There are few data regarding the prevalence of CKD in South Africa, though crude estimates range from 6.4% to 17.3%.(7,8)

Despite a growing population of patients with CKD in South Africa, access to care remains severely restricted for many.(9) This is especially true for those who progress to kidney failure (KF) and require chronic kidney replacement therapy (KRT).(9) South Africa has the highest Gini coefficient (0.63) globally, reflecting significant wealth disparities.(10) As a result, relatively few (15%) can afford private medical insurance, with most (85%) of the population are reliant on a resource-poor public healthcare sector, where KRT is strictly rationed (Figure 1).(9,11) The treatment rate of chronic dialysis in the private sector is more than fifteen times higher than that in the public sector, with the gap only increasing. (9) Transplantation rates are low,

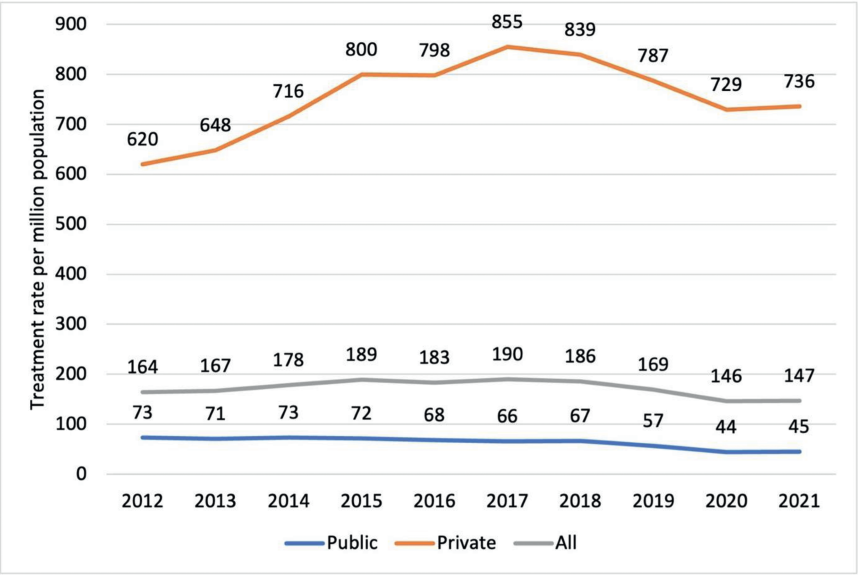

Figure 1: Trends in the prevalence of kidney replacement therapy over the last decade in South Africa (South African Renal Registry data from 2012–2021)

leading to a bottleneck in dialysis programmes, particularly in the public sector. (9,12) Consequently, the stagnation in the availability of dialysis slots means that KRT must be rationed in the public sector.

The fact that many South Africans with CKD will not have access to KRT emphasises the importance of retarding disease progression. The introduction of renin-angiotensin-system inhibitors (RASi) as a means of renal protection represented an essential milestone in treating CKD.(13) However, there were no comparable advances for nearly twenty years after that. In the last decade, several newer therapies have shown promise. In this review, we discuss some of the most important recent advancements in managing CKD and the applicability and accessibility of these therapies in the South African context. These advances will be divided into those relevant to the pre-KRT CKD population and treatments for patients on KRT.

ADVANCES IN THE MANAGEMENT OF PRE-KRT CKD

There have been many advances in managing CKD over past 40 years. Figure 2 highlights the chronology of these advances during this period.

Newer antidiabetic agents

Perhaps the most notable amongst the newer therapies are the sodium-glucose-transporter-2 (SGLT2) inhibitors. The exact mechanism by which they confer renal protection has yet to be fully understood and is likely to be multifactorial.(14,15) Broadly, they are thought to have specific effects on renal haemodynamics, tubulointerstitial function, and systemic effects that benefit the kidney. By inhibiting the absorption of sodium (and glucose) via the SGLT-2 cotransporter in the proximal tubule, increased sodium delivery at the macula densa results in activation of tubuloglomerular feedback and reduced intraglomerular pressure, mitigating hyperfiltration. In addition, reducing glucose concentration in proximal tubular cells and the interstitium may reduce oxidative stress, glucose-mediated fibrosis, and renal congestion. Additional benefits, such as blood pressure reduction associated with SGLT2 inhibitors, may be related to insulin resistance and natriuresis improvements.(14,15) Finally, there is evidence of an "aestivation-like" response associated with SGLT2 inhibitor use, whereby amino acids and fatty acids are preferentially used as energy sources. The net effect is a reduced metabolic rate, with resultant renoprotective effects at the glomerulus level and renal tubular epithelial cells.(15) Large clinical trials have consistently shown that SGLT2 inhibitors slow the progression of CKD and reduce the number of hospitalisations and deaths due to renal and cardiovascular disease in both patients with and without diabetes mellitus.(16) Firstly, the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) study, aimed primarily at assessing the effect of an SGLT-2 inhibitor (empagliflozin) on cardiovascular outcomes, also reported on a composite renal outcome, which comprised a doubling of serum creatinine, initiation of KRT and death from renal causes. Patients who received empagliflozin in addition to the standard of care had a significantly lower risk of the composite renal outcome.(17) Similarly, the CREDENCE (Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy) trial demonstrated a lower risk of worsening kidney function, progression to

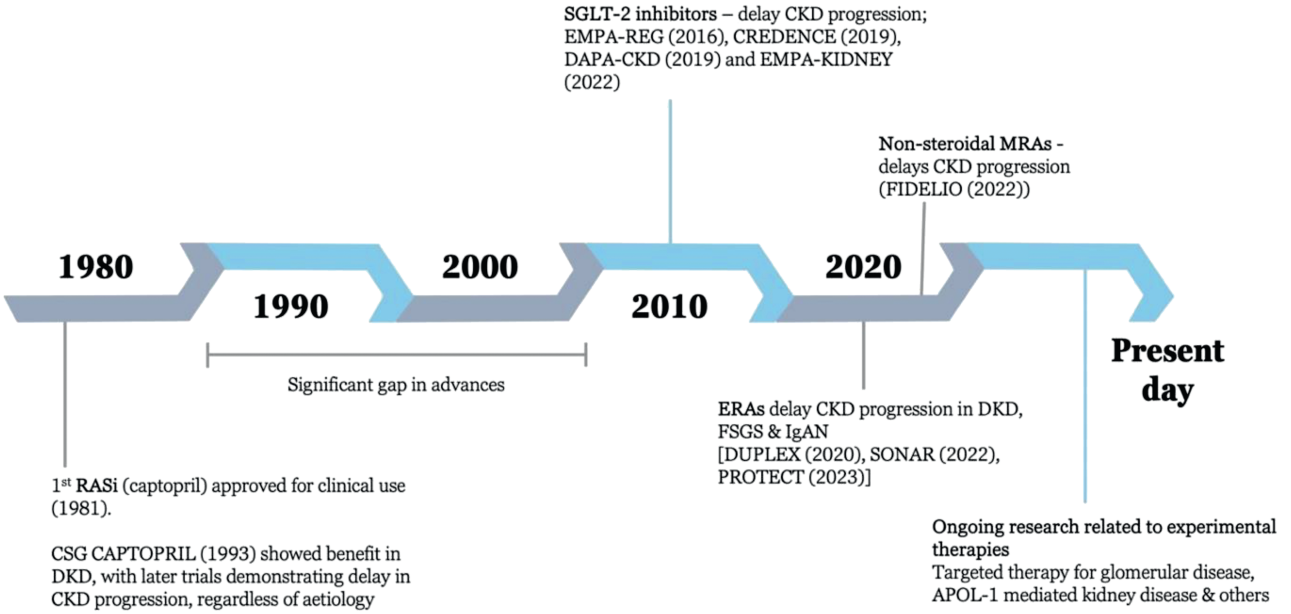

Figure 2: Milestones in the management of CKD over the past 40-years
Abbreviations: CKD, chronic kidney disease; RASi, renin-angiotensin-system inhibitors; DKD, diabetic kidney disease; SGLT-2, sodium-glucose co-transporter-2; ERAs, endothelin receptor antagonists; FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; MRAs, mineralocorticoid receptor antagonists; APOL-1, apolipoprotein-1.

kidney failure and death from renal causes amongst patients with type 2 diabetes mellitus and diabetic kidney disease (DKD) who received canagliflozin.(18) The DAPA-CKD (Dapagliflozin in Patients with Chronic Kidney Disease) and EMPA-KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin) trials were not limited to patients with DKD and reported comparable benefits associated with SGLT-2 inhibitor use across a broader spectrum of patients with CKD.(19,20)

Other anti-diabetic agents with potentially renoprotective effects include glucagon-like-peptide-1 (GLP-1) receptor agonists and dipeptidyl-peptidase-4 (DPP-4) inhibitors (also known as gliptins). Much like SGLT-2 inhibitors, the precise mechanisms by which they confer renoprotection are unclear and probably pleiotropic.(21,22) The benefit of GLP-1 receptor agonist use in DKD is mainly driven by a reduction in albuminuria, with reductions in oxidative stress, inflammation, and fibrosis demonstrated in animal studies. (21) In vitro studies suggest that DPP-4 inhibitors may slow down the progression of DKD through similar mechanisms, with their antifibrotic effects the most notable.(22) Notwithstanding, there are limited data on clinically meaningful outcomes using these agents; clinical trials, limited by relative-short follow-up periods, have, thus far, only demonstrated reductions in albuminuria without reducing the progression of CKD or risk of death.(22)

In South Africa, the prevalence of diabetes mellitus is estimated at 11.3% amongst adults and is on an upward trajectory.(23,24) Diabetic kidney disease was the third most common secondary glomerular disease (14.4%) in a study describing the patterns of biopsy-proven kidney disease at a tertiary hospital in the Western Cape, South Africa.(25) It is the third most common primary renal diagnosis (13.3%) amongst patients receiving KRT in South Africa.(9) Therefore, there is little doubt regarding the utility of the drugs mentioned above, especially SGLT2 inhibitors, in South Africa. A recent African Association of Nephrology steering committee meeting concluded that SGLT2 inhibitors may play a pivotal role in the prevention of the progression of CKD to KF in Africa since there is a lack of optimal screening and effective detection of CKD on the continent, as well as a limited access to KRT.(26) While the prescription of SGLT-2 inhibitors is commonplace in the South African private healthcare sector, access to these drugs is extremely limited in the public healthcare sector, primarily because of financial constraints.

Non-steroidal mineralocorticoid receptor antagonists

The deleterious consequences of mineralocorticoid receptor overactivation in DKD and CKD include glomerular hypertrophy and scarring, reduced renal blood flow, and inflammation, leading to the progression of kidney disease. Finerenone, a nonsteroidal MRA, may attenuate these processes by preventing the binding of aldosterone and the mineralocorticoid receptor.(27)

The FIDELIO-DKD (Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes) trial demonstrated a reduction in CKD progression and

death from both renal and cardiovascular causes amongst patients using finerenone.(28) Unfortunately, finerenone is not available in South Africa's public healthcare sector.

Endothelin receptor antagonists

Endothelin-1 (ET-1), a polypeptide with potent vasoconstrictive properties, is produced by endothelium and a variety of cells in the kidney and cardiovascular system.(29) By binding to endothelin-A (ETA) receptors in the kidney, it results in efferent and afferent arteriolar vasoconstriction with resultant glomerular hypertension. Activation of the ETA receptors on podocytes leads to cytoskeletal disruption and proteinuria. Furthermore, ET-1 contributes to mesangial expansion and inflammatory cell infiltration in the glomerulus.(29) In contrast, activation of endothelin-B (ETB) receptors results in efferent arteriolar vasodilation. Moreover, ETB receptor binding results in natriuretic, anti-inflammatory and antifibrotic effects.(29) Endothelin receptor antagonists (ERAs) bind endothelin receptors, abrogating the vasomotor, inflammatory and fibrotic consequences of ETA activation.(29) Theoretically, selective ETA receptor antagonists (e.g. atrasentan) should preserve the beneficial effects of ETB agonism. Paradoxically, overactivation of ETB receptors may result in fluid retention through increased vascular permeability, vasodilatation and RAS activation.(29)

Several clinical trials have demonstrated a reduction in albuminuria with ERA use. In addition, the SONAR (Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease) trial demonstrated a reduction in CKD progression compared with placebo. (30) Although most of these trials studied the effect of ERAs in patients with DKD, the DUPLEX (Study of Sparsentan in Patients With Primary Focal Segmental Glomerulosclerosis) trial demonstrated higher rates of partial remission amongst patients with focal segmental glomerulosclerosis (FSGS) who used sparsentan, a dual endothelin-angiotensin receptor blocker, compared to those who used angiotensin-receptor blockers alone. (31) Similarly, the PROTECT (a Study of the Effect and Safety of Sparsentan in the Treatment of Patients With IgA Nephropathy) trial showed significant antiproteinuric effects in patients with IgA nephropathy.(32)

DKD and FSGS are common in South Africa, with the latter reported as the second most common, biopsy-proven primary glomerular disease.(25) Despite promising results in these populations, ERAs still need to be registered in South Africa.

Advances in the treatment of glomerular diseases

Although a comprehensive appraisal of the glomerular disease treatment is beyond this review's scope, we will highlight some key developments in the last few years. As our understanding of the molecular mechanisms underlying glomerular disease evolves, targeted therapies have become more prominent.(33) They include antibody-like molecules that bind to specific membrane receptors and small molecules that disrupt intracellular signalling. These therapies target the following elements: B- and plasma cell survival, the complement system, and fibrogenic cytokines.(33)

B- and plasma cell-depleting agents

Rituximab is a monoclonal antibody which binds CD20, a receptor found on all B-cells, resulting in B-cell depletion. The FDA has approved its use in ANCA-associated vasculitis.(33) Furthermore, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend its use in the management of primary membranous nephropathy (MN) and frequently relapsing or steroid-dependent minimal change disease (MCD).(34)

The B-cell activation factor (BAFF) pathway has emerged as a target for biologic therapy. With another transmembrane protein called a proliferation-inducing ligand (APRIL), a B-cell activating factor belonging to the TNF family, BAFF mediates B-cell survival and differentiation.(33) Belimumab, which targets BAFF, has been added to the KDIGO guidelines for managing lupus nephritis (LN).(35) This recommendation is based on the BLISS-LN trial, which reported higher remission and lower relapse rates in patients who received belimumab in addition to standard-of-care (SOC) compared to those who received SOC only.(36)Sibeprenlimab, which targets the APRIL transmembrane protein, has shown promise in treating IgA nephropathy.(33) Phase II of the ongoing ENVISION (Safety and Efficacy Study of VIS649 for IgA Nephropathy) trial showed a significant reduction in proteinuria in those treated with sibeprenlimab compared to those receiving placebo. (37)Daratumumab, a plasma cell-depleting monoclonal antibody targeting CD38, has been shown to reduce proteinuria and preserve kidney function in patients with multiple myeloma and proliferative glomerulonephritis (including monoclonal immunoglobulin deposition disease and C3 glomerulopathy).(33)

Complement pathway inhibitors

Dysregulation of the complement system has been implicated in many glomerular diseases.(33) Eculizumab, a monoclonal antibody targeting C5 with resultant terminal complement inhibition, has been shown to improve platelet counts and improve kidney function in patients with atypical haemolytic-uraemic syndrome.(38)

Small-molecules which target the complement system have also shown promising results.(33) Avacopan, a C5a receptor antagonist, may be a more tolerable substitute for conventional corticosteroids in the management of ANCA-associated vasculitis.(39) Iptacopan, a factor B inhibitor, has been studied in the treatment of C3 glomerulopathy and IgA nephropathy, resulting in significant reductions in proteinuria.(40,41) Immune complex-associated

mesangiocapillary (also known as membranoproliferative) glomerulonephritis has been reported to be the most common primary glomerular pattern of injury identified on kidney biopsies in the Western Cape province of South Africa.(42) Pegcetacopan, which inhibits the activation of complement pathways by binding C3 and C3b, is currently under investigation in several trials for the treatment of this condition (NCT05067127, NCT04572854, NCT05809531).(43–45)

Antifibrotics

Fibrosis represents the final common pathway of many glomerular disorders. Aside from SGLT2 inhibitors and finerenone, newer therapies with antifibrotic properties such as chemokine receptor antagonists (e.g pirfenidone), are under investigation, with several phase II trials presently underway.(33)

Other notable developments include the addition of calcineurin inhibitors for the management of lupus nephritis. The 2024 KDIGO guidelines suggest voclosporin in addition to mycophenolate mofetil and corticosteroids in selected patients with proliferative lupus nephritis, based on the findings of Aura-LV trial.(35) Another potential treatment avenue for autoimmune diseases like lupus nephritis involves the use of chimeric antigen receptor T-cells (CAR-T), which are harvested and genetically engineered from T-cells to target autoreactive B-cells responsible for producing antibodies.(46)

These developments are pertinent to South Africa, which faces a substantial burden of glomerular disease. It is the fourth most common renal diagnosis amongst patients receiving KRT in South Africa.(9) Aside from rituximab, none of the newer biologic therapies are registered for use in South Africa. In addition, their costs are likely to be prohibitive, particularly in the public healthcare sector. Although voclosporin is unavailable in South Africa, alternative recommendations such as tacrolimus are accessible in both the private and public sectors.

Polycystic kidney disease

Tolvaptan, which is a vasopressin-2 receptor (V2R) antagonist, was approved by the FDA in 2017, following the results of REPRISE (Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease) trial. The findings of this study were in line with the earlier TEMPO (Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease [ADPKD]) trial; that is, tolvaptan has been shown to slow the loss of kidney function in patients with ADPKD when compared to placebo.(47) In vitro studies suggest that, by binding V2R receptors, tolvaptan inhibits cyst growth through cAMP-dependent pathways.(48)

Although the prevalence of ADPKD in South Africa is unknown, 3.3% of patients on KRT have ADPKD.(9) The "vaptans" are not registered for use in South Africa.

Human-immunodeficiency virus-associated nephropathy (HIVAN) and APOL-1 mediated kidney disease

The prevalence of human immunodeficiency virus (HIV) infection in South Africa has been estimated at 12.7%, making it a significant cause of kidney disease in South Africa.(49) In a study on biopsy-proven kidney diseases at a tertiary hospital in the Western Cape, HIVAN was the second most common pattern of disease. However, a spectrum of HIV-associated kidney diseases other than HIVAN has emerged in recent years.(25,50) There is a known association between the high-risk allele, APOL-1, and the risk of developing HIVAN.(51) An evolved understanding of APOL-1-mediated mechanisms of kidney disease has given rise to several experimental therapies.(52) A recent phase IIa study that investigated the effect of inaxaplin, an inhibitor of the APOL-1 channel, in patients who had proteinuric kidney disease and two APOL-1 variants (G1 or G2) or FSGS, reported a nearly 50% reduction in proteinuria after 13 weeks of therapy.(53) Since sSA has a high prevalence of APOL-1 mediated kidney disease, this drug may have an essential role in the treatment of CKD, but highly active antiretroviral therapy (HAART) remains the cornerstone of therapy at present.

ADVANCEMENTS IN THE MANAGEMENT OF PATIENTS ON KRT

Anaemia management in patients on KRT

Reduced oxygen tension within the kidneys is common in CKD. Under hypoxic conditions, hypoxia-inducible factor (HIF) promotes the transcription of many genes, leading to increased erythropoietin (EPO) production. By preventing the degradation of HIF by prolyl hydroxylase, HIF-PH inhibitors enhance hypoxia-mediated EPO production. Furthermore, they have anti-inflammatory properties, ameliorating functional iron deficiency.(54) HIF-PH inhibitors, such as roxadustat, have shown benefits in pre-KRT and KRT populations.(55) Several trials have found the efficacy and safety of roxadustat to be comparable to erythropoiesis-stimulating agents (ESAs) in both non-dialysis dependent CKD and those on dialysis.(55–57)

Roxadustat is registered for use in the management of CKD-related anaemia in South Africa, though its use is largely limited to the private healthcare sector due to cost.

Haemodiafiltration

Theoretically, haemodiafiltration (HDF), which essentially combines standard, high-flux haemodialysis (HD) with large-volume convection, represents a superior modality for solute clearance, and may offer better haemodynamic tolerability.(58) The CONVINCE (Effect of Hemodiafiltration or Hemodialysis on Mortality in Kidney Failure) trial reported that compared to those receiving high-flux HD, patients on HDF had lower all-cause mortality, with the most notable

benefits in older patients, and those without pre-existing diabetes mellitus or cardiovascular disease. While a statistically significant difference in overall mortality was noted, the fragility index stood at three, suggesting that the study would have lost significance if three patients in the HDF group developed the primary outcome. Given high costs associated with its use and the requirement for ultrapure water, HDF is yet to replace HD as the standard of care. However, it may offer greater benefit in certain subgroups. (58) Haemodiafiltration is available in South Africa, though there are no published data on the prevalence of its use.

ABO incompatible transplantation

In the past, ABO incompatibility (ABOi) was an absolute contraindication for kidney transplantation. However, with advances in desensitisation protocols and immunosuppressive therapy, ABOi kidney transplant outcomes have improved significantly over the past two decades. This makes it a potentially important means of expanding the donor pool.

Nephrologists at Groote Schuur Hospital, a tertiary centre in the Western Cape, recently reported three cases of ABOi kidney transplants using a newly acquired immunoadsorption column.(59) While initial findings appear encouraging, larger studies assessing longer-term patient and kidney allograft outcomes are necessary before ABOi kidney transplants can be established as standard practice.

Xenotransplantation

The first successful xenotransplantation of a genetically edited porcine kidney into a human recipient was performed at Massachusetts General Hospital on 16 March 2024. Unfortunately, the patient demised two months following transplantation. The cause of death has not been reported. (60) Given the increasingly long waiting lists of patients requiring kidney transplantation and a high-mortality rate while on the waiting list, xenotransplantation could become a valuable option for patients with kidney failure. However, xenotransplantation is a relatively new science and long-term data on outcomes are needed before it becomes an acceptable alternative to allotransplantation. Furthermore, the societal acceptance of xenotransplantation may be hampered by ethical, cultural, and religious controversies.(61)

CONCLUSION

Promising developments in the management of CKD have emerged after a lengthy hiatus. Many of these therapies have materialised in the context of research related to diabetes mellitus. Others have emerged from a more sophisticated understanding of molecular mechanisms of kidney disease. Unfortunately, most novel therapies for CKD are either unavailable in South Africa, or prohibitively expensive, limiting their use in the public healthcare sector, upon which most South Africans with CKD are dependent.

There are many, complex barriers limiting the access and use of novel therapies for CKD in South Africa, ranging from governmental policies to market forces. Strategies for improving access to these therapies include; implementing health policies which recognise CKD as a health priority, universal health coverage, and minimising reliance on pharmaceutical imports by investing in the local pharmaceutical industry. (62,63) Although its structuring faces criticism, the National Health Insurance (NHI) is now an inevitability in South Africa and it may bridge the gap in access to therapies previously out of reach in the public healthcare sector due to cost. (64) Aside from cost, there is evidence to suggest that even widely available therapies, such as RASi, may be withheld from patients with CKD due to prescription inertia and knowledge gaps on the part of clinicians, emphasising the importance of professional education and improving the working conditions of healthcare workers in the country.(63) As the proportion of underserved South African patients with CKD grows, greater effort is required at all strata of the health system, to ensure that we can translate knowledge of new therapies for the management of CKD into daily clinical practice more readily.

REFERENCES

1. Stevens PE, Ahmed SB, Carrero JJ, et al. KDIGO 2024 Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2024;105(4):S117–S314.
2. Davids MR, Chothia M-Y, Wearne N, Davidson B, McCulloch M. Global consideration in kidney disease: Africa. In: Moura-Neto JA, Divino-Filho JC, Ronco C, editors. Nephrology worldwide. Cham: Springer; 2023:1–49.
3. Kaze AD, Ilori T, Jaar BG, Echouffo-Tcheugui JB. Burden of chronic kidney disease on the African continent: a systematic review and meta-analysis. BMC Nephrol. 2018;19:1–11.
4. Abd ElHafeez S, Bolignano D, D'Arrigo G, et al. Prevalence and burden of chronic kidney disease among the general population and high-risk groups in Africa: a systematic review. BMJ Open. 2018;8(1):e015069.
5. Stanifer JW, Jing B, Tolan S, et al. The epidemiology of chronic kidney disease in sub-Saharan Africa: a systematic review and meta-analysis. Lancet Glob Health. 2014;2(3):e174–e181.
6. Mayosi BM, Flisher AJ, Lalloo UG, et al. The burden of non-communicable diseases in South Africa. Lancet. 2009;374(9693):934–947.
7. Adeniyi AB, Laurence CE, Volmink JA, Davids MR. Prevalence of chronic kidney disease and association with cardiovascular risk factors among teachers in Cape Town, South Africa. Clin Kidney J. 2017;10(3):363–369.
8. Matsha TE, Yako YY, Rensburg MA, et al. Chronic kidney diseases in mixed ancestry South African populations: prevalence, determinants and concordance between kidney function estimators. BMC Nephrol. 2013;14:1–10.
9. Davids MR, Marais N, Sebastian S, Jardine T, Jacobs JC. South African Renal Registry Annual Report 2021. Afr J Nephrol. 2023;26(1):83–94.
10. Sulla V, Zikhali P. Overcoming poverty and inequality in South Africa: an assessment of drivers, constraints and opportunities. The World Bank; 2018. Published March

2018. Accessed 7 April 2024. https://documents1.worldbank.org/curated/en/530481521735906534/pdf/Overcoming-Poverty-and-Inequality-in-South-Africa-An-Assessment-of-Drivers-Constraints-and-Opportunities.pdf
11. Coovadia H, Jewkes R, Barron P, Sanders D, McIntyre D. The health and health system of South Africa: historical roots of current public health challenges. Lancet. 2009;374(9692):817–834.
12. Moosa M. The state of kidney transplantation in South Africa. S Afr Med J. 2019;109(4):235–240.
13. Murakami T, Iwamoto T, Yasuda G, et al. Role of renin–angiotensin system inhibitors in retardation of progression of end-stage renal failure: a retrospective study. Clin Exp Nephrol. 2016;20:603–610.
14. Skrabic R, Kumric M, Vrdoljak J, et al. SGLT2 inhibitors in chronic kidney disease: from mechanisms to clinical practice. Biomedicines. 2022;10(10):2458.
15. Nishiyama A, Kitada K. Possible renoprotective mechanisms of SGLT2 inhibitors. Front Med. 2023;10:1115413.
16. Rhee JJ, Jardine MJ, Chertow GM, Mahaffey KW. Dedicated kidney disease-focused outcome trials with sodium-glucose cotransporter-2 inhibitors: lessons from CREDENCE and expectations from DAPA-HF, DAPA-CKD, and EMPA-KIDNEY. Diabetes Obes Metab. 2020;22:46–54.
17. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med. 2016;375(4):323–334.
18. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380(24):2295–2306.
19. Heerspink HJ, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436–1446.
20. Group E-KC. Empagliflozin in patients with chronic kidney disease. N Engl J Med. 2023;388(2):117–127.
21. Kawanami D, Takashi Y. GLP-1 receptor agonists in diabetic kidney disease: from clinical outcomes to mechanisms. Front Pharmacol. 2020;11:967.
22. Daza-Arnedo R, Rico-Fontalvo J-E, Pájaro-Galvis N, et al. Dipeptidyl peptidase-4 inhibitors and diabetic kidney disease: a narrative review. Kidney Med. 2021;3(6):1065–1073.
23. Pheiffer C, Pillay-van Wyk V, Turawa E, et al. Prevalence of type 2 diabetes in South Africa: a systematic review and meta-analysis. Int J Environ Res Public. 2021;18(11):5868.
24. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119.
25. Esmail AM, Bates WD, Amirali MH, Jardine T, Davids MR. Patterns of biopsy-proven kidney disease amongst South African adults from 1995 to 2017. Afr J Nephrol. 2023;26(1):9–16.
26. Jarraya F, Niang A, Bagha H, et al. The role of sodium-glucose cotransporter-2 inhibitors in the treatment paradigm of CKD in Africa: an African Association of Nephrology Panel position paper. Kidney Int Rep. 2024;9(3):526–548.
27. Lv R, Xu L, Che L, et al. Cardiovascular-renal protective effect and molecular mechanism of finerenone in type 2 diabetic mellitus. Front Endocrinol. 2023;14:1125693.
28. Rossing P, Agarwal R, Anker SD, et al. Efficacy and safety of finerenone in patients with chronic kidney disease and type 2 diabetes by GLP-1RA treatment: a subgroup analysis from the FIDELIO-DKD trial. Diabetes Obes Metab. 2022;24(1):125–134.
29. Chung EYM, Badve SV, Heerspink HJL, Wong MG. Endothelin receptor antagonists in kidney protection for diabetic kidney disease and beyond? Nephrology (Carlton). 2023;28(2):97–108.
30. Heerspink HJ, de Zeeuw D. Endothelin receptor antagonists for kidney protection: lessons from the SONAR trial. Clin J Am Soc Nephrol. 2022;17(6):908–910.
31. Komers R, Diva U, Inrig JK, et al. Study design of the phase 3 sparsentan versus irbesartan (DUPLEX) study in patients with focal segmental glomerulosclerosis. Kidney Int Rep. 2020;5(4):494–502.
32. Heerspink HJL, Radhakrishnan J, Alpers CE, et al. Sparsentan in patients with IgA nephropathy: a prespecified interim analysis from a randomised, double-blind, active-controlled clinical trial. Lancet. 2023;401(10388):1584–1594.
33. Lin Y-C, Gau T-S, Jiang Z-H, et al. Targeted therapy in glomerular diseases. J Formos Med Assoc. 2024;123(2):149–158.
34. Rovin BH, Adler SG, Barratt J, et al. Executive summary of the KDIGO 2021 guideline for the management of glomerular diseases. Kidney Int. 2021;100(4):753–779.
35. Rovin BH, Ayoub IM, Chan TM, et al. Executive summary of the KDIGO 2024 clinical practice guideline for the management of lupus nephritis. Kidney Int. 2024;105(1):31–34.
36. Furie R, Rovin B, Houssiau F, et al. OP0164 BLISS-LN: a randomised, double-blind, placebo-controlled phase 3 trial of intravenous belimumab in patients with active lupus nephritis. Ann Rheum Dis. 2020;79:103–103.
37. Mathur M, Barratt J, Chacko B, et al. A phase 2 trial of sibeprenlimab in patients with IgA nephropathy. N Engl J Med. 2024;390(1):20–31.
38. Legendre C, Licht C, Muus P, et al. Terminal complement inhibitor eculizumab in atypical hemolytic–uremic syndrome. N Engl J Med. 2013;368(23):2169–2181.
39. Thorley J. FDA approves avacopan for ANCA-associated vasculitis. Lancet Rheumatol. 2022;4(1):e21.
40. Wong E, Nester C, Cavero T, et al. Efficacy and safety of iptacopan in patients with C3 glomerulopathy. Kidney Int Rep. 2023;8(12):2754–2764.
41. Barratt J, Rovin B, Zhang H, et al. POS-546 efficacy and safety of iptacopan in IgA nephropathy: results of a randomized double-blind placebo-controlled phase 2 study at 6 months. Kidney Int Rep. 2022;7(2):S236.
42. Chothia M-Y, Panday AS, Coetzee L, Bates W. Outcomes of immunoglobulin-associated mesangiocapillary glomerulonephritis: a South African experience. Nephrology. 2020;25(10):765–774.
43. Apellis Pharmaceuticals I. Phase III study assessing the efficacy and safety of pegcetacoplan in patients with C3 glomerulopathy or immune-complex membranoproliferative glomerulonephritis. Updated 12 March 2024. Accessed 12 April 2024, https://classic.clinicaltrials.gov/show/NCT05067127
44. Apellis Pharmaceuticals I. Study assessing the safety and efficacy of pegcetacoplan in post-transplant recurrence of C3G or IC-MPGN. Updated 6 March 2024. Accessed 12 April 2024, https://classic.clinicaltrials.gov/show/NCT04572854
45. Apellis Pharmaceuticals I. An open-label, nonrandomized, multicenter extension study to evaluate the long-term safety and efficacy of pegcetacoplan in participants with C3

glomerulopathy or immune-complex membranoproliferative glomerulonephritis. Updated 12 March 2024. Accessed 12 April 2024, https://classic.clinicaltrials.gov/show/NCT05809531
46. Müller F, Taubmann J, Bucci L, et al. CD19 CAR T-Cell therapy in autoimmune disease – a case series with follow-up. N Engl J Med. 2024;390(8):687–700.
47. Müller R-U, Messchendorp AL, Birn H, et al. An update on the use of tolvaptan for ADPKD: consensus statement on behalf of the ERA Working Ggroup on inherited kidney disorders (WGIKD), the European Rare Kidney Disease Reference Network (ERKNet) and Polycystic Kidney Disease International (PKD-International). Nephrol Dial Transpl. 2021;10.
48. Nobakht N, Hanna RM, Al-Baghdadi M, et al. Advances in autosomal dominant polycystic kidney disease: a clinical review. Kidney Med. 2020;2(2):196–208.
49. Shean Y. The 6th South African National HIV Prevalence, Incidence, Behaviour and Communication Survey (SABSSM VI): 20 years of strategic HIV and public health data. Launch of the key findings. Published 27 November 2023. Accessed 7 April 2024. https://hsrc.ac.za/special-projects/sabssm-survey-series/sabssmvi-media-pack-november-2023/
50. Wearne N, Manning K, Price B, et al. The evolving spectrum of kidney histology in HIV-positive patients in South Africa. Kidney Int Rep. 2023;8(5):1087–1096.
51. Waziri B, Raji YE, Ekrikpo UE, Naicker S. Apolipoprotein L1 gene variants and kidney disease in patients with HIV: a systematic review and meta-analysis. J Nephrol. 2023;36(4):1119–1134.
52. Vasquez-Rios G, De Cos M, Campbell KN. Novel therapies in APOL-1 mediated kidney disease: from molecular pathways to therapeutic options. Kidney Int Rep. 2023;8(11):2226–2234.
53. Egbuna O, Zimmerman B, Manos G, et al. Inaxaplin for proteinuric kidney disease in persons with two APOL1 variants. N Engl J Med. 2023;388(11):969–979.
54. Haase VH. Hypoxia-inducible factor-prolyl hydroxylase inhibitors in the treatment of anemia of chronic kidney disease. Kidney Int Suppl. 2021;11(1):8–25.
55. Chen N, Hao C, Peng X, et al. Roxadustat for anemia in patients with kidney disease not receiving dialysis. N Engl J Med. 2019;381(11):1001–1010.
56. Barratt J, Andric B, Tataradze A, et al. Roxadustat for the treatment of anaemia in chronic kidney disease patients not on dialysis: a phase 3, randomized, open-label, active-controlled study (DOLOMITES). Nephrol Dial Transpl. 2021;36(9):1616–1628.
57. Choukroun G, Harkavyi A, Santos V, Jiletcovici A, Vecchio LD. Efficacy and safety of roxadustat in patients with anemia of dialysis-dependent CKD with or without inflammation: a pooled analysis of 4 phase 3 studies. Nephrol Dial Transpl. 2023;38.
58. Blankestijn PJ, Vernooij RW, Hockham C, et al. Effect of hemodiafiltration or hemodialysis on mortality in kidney failure. N Engl J Med. 2023;389(8):700–709.
59. Barday Z. ABO-incompatible kidney transplantation using immunoadsorption columns: first experiences in South Africa. S Afr Med J. 2024:e1326–e1326.
60. Chase B. World's first genetically-edited pig kidney transplant into living recipient performed at Massachusetts general hospital. Massachusetts General Hospital. Published 21 March 2024. Accessed 7 April 2024. https://www.massgeneral.org/news/press-release/worlds-first-genetically-edited-pig-kidney-transplant-into-living-recipient
61. Rollin BE. Ethical and societal issues occasioned by xenotransplantation. Animals (Basel). 2020;10(9):1965.
62. Ahen F, Salo-Ahen OM. Governing pharmaceutical innovations in Africa: inclusive models for accelerating access to quality medicines. Cogent Med. 2018;5(1):1500196.
63. Luyckx VA, Tuttle KR, Abdellatif D, et al. Mind the gap in kidney care: translating what we know into what we do. Kidney Int. 2024;105(3):406–417.
64. Perumal-Pillay VA, Suleman F. Drawing lessons from the standard treatment guidelines and essential medicines list concept in South Africa as the country moves towards national health insurance. S Afr Fam Pract. 2021;63(1):e1–e3.