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Therapeutic Inhibition of VEGF Signaling and Associated Nephrotoxicities

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ABSTRACT

Inhibition of vascular endothelial growth factor A (VEGFA)/vascular endothelial growth factor receptor 2 (VEGFR2) signaling is a common therapeutic strategy in oncology, with new drugs continuously in development. In this review, we consider the experimental and clinical evidence behind the diverse nephrotoxicities associated with the inhibition of this pathway. We also review the renal effects of VEGF inhibition's mediation of key downstream signaling pathways, specifically MAPK/ERK1/2, endothelial nitric oxide synthase, and mammalian target of rapamycin (mTOR). Direct VEGFA inhibition *via* antibody binding or VEGF trap (a soluble decoy receptor) is associated with renal-specific thrombotic microangiopathy (TMA). Reports also indicate that tyrosine kinase inhibition of the VEGF receptors is preferentially associated with glomerulopathies such as minimal change disease and FSGS. Inhibition of the downstream pathway RAF/MAPK/ERK has largely been associated with tubulointerstitial injury. Inhibition of mTOR is most commonly associated with albuminuria and podocyte injury, but has also been linked to renal-specific TMA. In all, we review the experimentally validated mechanisms by which VEGFA-VEGFR2 inhibitors contribute to nephrotoxicity, as well as the wide range of clinical manifestations that have been reported with their use. We also highlight potential avenues for future research to elucidate mechanisms for minimizing nephrotoxicity while maintaining therapeutic efficacy.

J Am Soc Nephrol 30: 187–200, 2019. doi: https://doi.org/10.1681/ASN.2018080853

Inhibitors of vascular development were first investigated as potential chemotherapeutic agents on the basis of study findings from the late 20th century regarding the critical role of angiogenesis in tumor development and growth.[1] Subsequent investigations led to the discovery of vascular endothelial growth factor A (VEGFA), an essential growth factor for angiogenesis.[2,3] Previous studies by Kim *et al.*[4] used murine cancer cell lines to show that treatment with an mAb against VEGFA decreased tumor growth, indicating a potential therapeutic role for VEGFA inhibition in cancer treatment. Beginning with the development of bevacizumab, a recombinant IgG mAb against VEGFA, inhibiting VEGF signaling proved to be a promising approach to halting neoplastic development.[5] Since then, many additional agents that block VEGF signaling and its downstream pathways have become available for the treatment of various cancers (Figure 1, i–vi).

Although these agents offer substantial benefit, both in the treatment of many solid tumors[6] as well as age-related macular degeneration,[7] their use is associated with significant nephrotoxicity.[8] Most commonly, pharmacologic VEGF inhibition has been associated with hypertension and proteinuria. Reports describe histologic changes in the kidney primarily as glomerular endothelial injury with thrombotic microangiopathy (TMA).[8] Nephrotic syndrome has also been observed,[9] with the clinical manifestations varying according to mechanism and direct target of VEGF inhibition.

Current VEGF inhibitors can be classified by their target of action in the VEGFA-VEGFR2 pathway: drugs that bind to VEGFA, sequester VEGFA, inhibit receptor tyrosine kinases (RTKs), or inhibit downstream pathways. A critical review of VEGFA-VEGFR2 signaling in the kidney is necessary to fully understand the mechanisms responsible for the nephrotoxicity associated with the oncological use of VEGF inhibition.

VEGF SIGNALING IN THE KIDNEY

Filtration of plasma in nephrons occurs in the glomerular capillary beds at the glomerular filtration barrier, which consists of three layers: fenestrated endothelial cells, basement membrane, and the

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ISSN : 1046-6673/3002-187

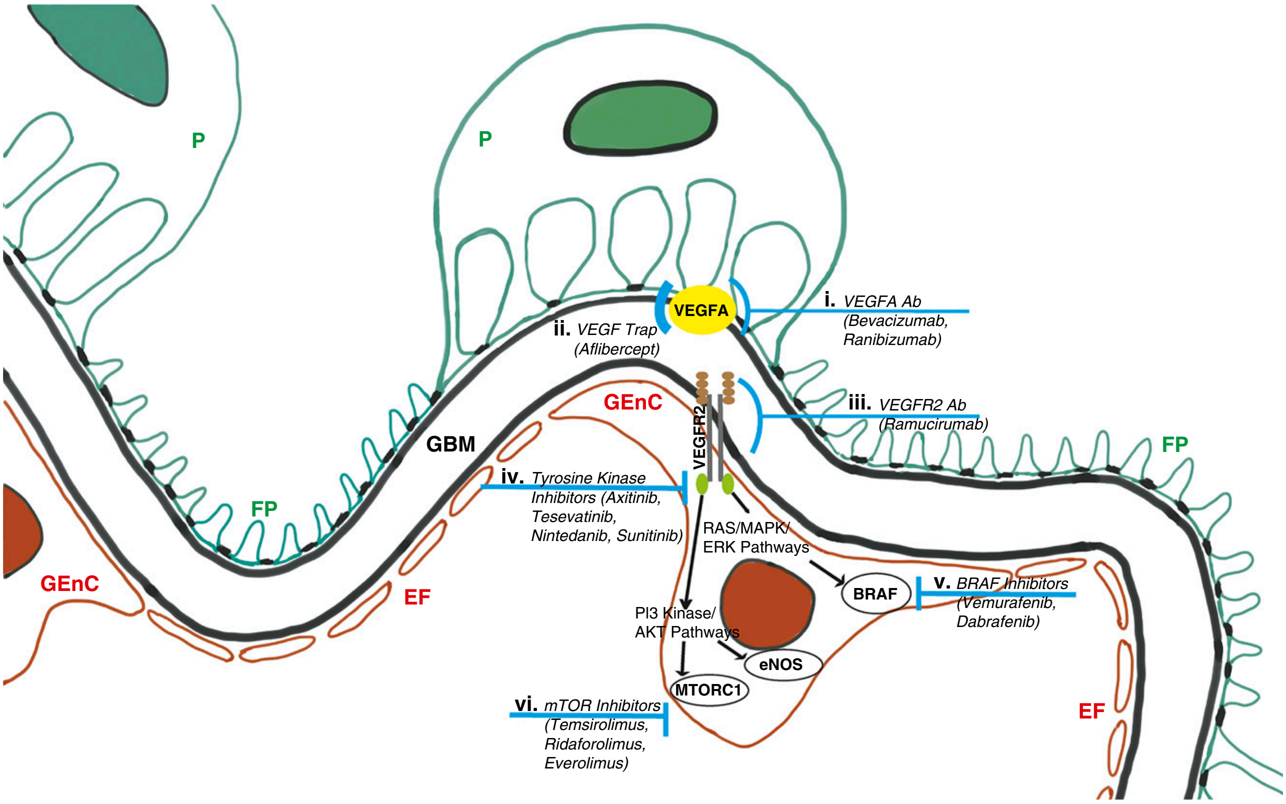

Figure 1. VEGFA-VEGFR2 signaling pathways and their pharmacological inhibition occur across the glomerular filtration barrier. VEGFA is released from podocytes and binds to its receptor (VEGFR2) on glomerular endothelial cells. (i) Bevacizumab and ranibizumab are mAbs against VEGFA and inhibit angiogenesis through IgG antibody interaction with all of its isoforms. (ii) Aflibercept is a recombinant fusion protein comprising binding domains for VEGFR1 and VEGFR2 attached to the Fc portion of human IgG1, and acts as a soluble decoy receptor or "VEGF trap." (iii) Ramucirumab is a fully humanized IgG1 mAb that specifically inhibits VEGFR2 by targeting its extracellular domain. (iv) TKIs such as sunitinib, pazopanib, sorafenib, and axitinib target VEGFR2, as well as interfere with the activity of additional RTKs such as PDGF receptor, fibroblast growth factor receptor, and EGF receptor, which all share a similar structure. (v) Agents such as vemurafenib and dabrafenib have been recently developed to specifically target B-Raf, a component of the intracellular MAPK/ERK intracellular pathway. (vi) mTOR inhibitors such as temsirolimus, ridaforolimus, and everolimus are used across several malignancies and act downstream of the phosphatidylinositide 3-kinase (PI3K)/AKT signal transduction pathway. Ab, antibody; BRAF, B-Raf Proto-Oncogene; EF, endothelial fenestrations; FP, foot process; GBM, glomerular basement membrane; GEnC, glomerular endothelial cell; P, Podocyte.

foot processes of visceral epithelial cells or podocytes. In the kidney, VEGFA is expressed by both podocytes[10] and renal tubular epithelial cells[11]; in humans, VEGFA$_{165}$ is the most abundant isoform.[12] VEGFA binds to one of two RTKs, VEGFR1 and VEGFR2[13]; although both receptors have been identified as playing an important role in angiogenesis, VEGFR2 has been more extensively studied, as it is responsible for a majority of VEGFA signaling and is abundantly distributed in stromal and malignant vascular tissues.[14,15] Both receptors are primarily localized in the glomerular and peritubular capillary endothelium.[11,16] Furthermore, VEGFR1 also exists in a soluble form, which acts as a decoy receptor, inhibiting VEGFA signaling,[17] and is the sole receptor for VEGFB.[12]

The functional diversity of VEGF receptors was initially elucidated by the creation of knockout mice. Mice deficient in *Vegfr2* die *in utero* from a defect in hematopoietic and endothelial cell development[18]; embryonic lethality of *Vegfr1* deletion is caused by endothelial cell overgrowth and disorganization.[19] These whole-body knockout mice underscore the key role of VEGF signaling in endothelial cell proliferation, migration, and permeability.[20]

The association of VEGFA overexpression[10] or reduction[8,21,10] with a wide range of glomerulopathies (Table 1) demonstrates that tight regulation of VEGFA signaling in the kidney is critical to glomerular development and the maintenance of mature glomerular function in both homeostasis and disease. For example, knockout of *Vegfa* during embryogenesis—including global homozygous or heterozygous knockout[22,23] or podocyte-specific knockout[10]—is uniformly lethal at or before birth. Mice with podocyte-specific partial deletion of *Vegfa* survive the perinatal period, but develop endotheliosis and renal failure by 9 weeks of age.[10]

In adult mice, inducible podocyte-specific *Vegfa* deletion produces renal-specific TMA, which recapitulates kidney biopsy

Table 1. Renal manifestations in VEGF-VEGFR transgenic murine models

Genotype	Model	Effects	Reference
Vegfa$^{-/-}$	Constitutive, whole-body deletion of *Vegfa*	Embryonically lethal	22,23
Vegfa$^{+/-}$	Constitutive, whole-body partial deletion of *Vegfa*	Embryonically lethal between days 11 and 12; defective yolk sac blood supply	22,23
Vegfr1$^{-/-}$	Constitutive, whole-body deletion of *Vegfr1*	Embryonically lethal because of endothelial cell overgrowth and disorganization	19
Vegfr2$^{-/-}$	Constitutive, whole-body deletion of *Vegfr2*	Embryonically lethal because of defect in hematopoietic and endothelial cell development	18
Nephrin-Cre; Vegfa$^{flox/flox}$	Constitutive deletion of *Vegfa* from podocytes	Perinatally lethal, mice die at birth or within 18 h with small glomeruli with few capillary loops	10
Nephrin-Cre; Vegfa$^{flox/+}$	Constitutive, partial deletion of *Vegfa* from podocytes	Endotheliosis, with eventual glomerulosclerosis and ESRD by 9–12 wk of age	10
Podocin-rtTA; TetO-Cre; Vegfa$^{flox/flox}$	Doxycycline-inducible deletion of *Vegfa* in podocytes	Renal thrombotic microangiopathy	8
Pax8-rtTA; TetO-Cre; Vegfa$^{flox/flox}$	Doxycycline-inducible deletion of *Vegfa* in tubular cells	Small, histologically normal kidneys with peritubular capillary rarefaction	11
Rosa-rtTA; TetO-Cre; Vegfr2$^{flox/flox}$	Doxycycline-inducible whole-body deletion of *Vegfr2*	Glomerular endothelial injury and ascites by 2.5 mo of age	24
Nephrin-Cre; Vegfr2$^{flox/flox}$	Constitutive deletion of *Vegfr2* from podocytes	Normal glomeruli and intact glomerular filtration barrier	24
Nephrin-VEGFA$_{164}$	Constitutive overexpression of the 164 isoform of VEGFA in podocytes	Collapsing glomerulopathy within 5 d of age	10
Podocin-rtTA: TetO-VEGF$_{164}$	Doxycycline-inducible overexpression of the 164 isoform of VEGFA in podocytes	Glomerulomegaly, mesangial expansion, foot process effacement	28

findings in individuals treated with VEGF inhibitors.[8] In contrast, mice with tubule-specific deletion of *Vegfa* had histologically normal kidneys with some peritubular capillary density loss,[11] emphasizing the essential role of podocyte-derived *Vegfa*. In studies of knockout mice, Sison *et al.*[24] highlighted the importance of paracrine VEGFA-VEGFR2 signaling between the podocyte and endothelial cell, showing that mice with podocyte-specific deletion of *Vegfr2* did not develop glomerulopathy, but those with whole-body inducible deletion of *Vegfr2* developed TMA, resembling mice lacking podocyte-specific *Vegfa*.

Although these experiments deemphasized autocrine VEGFA-VEGFR2 signaling in the podocyte, other studies have suggested the contrary. In cultured mouse podocytes, VEGFA treatment reduced apoptosis as well as upregulated podocin protein expression.[25] These results, suggesting podocyte autocrine dependence on secreted VEGFA, were corroborated in cultured human podocytes treated with the BRAF inhibitor dabrafenib and the MEK1 inhibitor trametinib, which strongly inhibited VEGF release and simultaneously increased albumin permeability.[26] Furthermore, biopsy specimens of patients treated with this combination therapy exhibited severe podocyte injury and effacement.[26]

Interestingly, in addition to developing renal-specific TMA, mice with inducible podocyte-specific *Vegfa* deletion exhibited reduced glomerular complement factor H (CFH) staining and increased glomerular C3 deposition.[27] The dependence of the expression of the complement regulatory protein CFH on VEGFA was also shown in cultured glomerular endothelial cells, where exogenous VEGF directly increased CFH expression.[27] This relationship was not seen in other endothelial cell lines, perhaps explaining the sensitivity of glomerular endothelial cells to alterations in VEGFA-VEGFR2 signaling.[27]

Increased VEGFA-VEGFR2 signaling also appears to have detrimental glomerular effects. Constitutive overexpression of *Vegfa*$_{164}$ in podocytes leads to collapsing glomerulopathy,[10] whereas its inducible overexpression results in glomerulomegaly with mesangial expansion.[28] Taken together, these findings suggest that maintenance of glomerular endothelial integrity relies heavily on tight regulation of paracrine VEGFA-VEGFR2 signaling between the podocyte and renal endothelium, and that administration of antiangiogenic therapeutics to disrupt this signaling and its downstream pathways directly results in renal endothelial injury, manifested primarily as proteinuria, hypertension, and renal-specific TMA.[8,29,30] However, it should be noted that histologic diagnosis of such injury is often limited because of the underutilization of kidney biopsies. In addition, these manifestations occur with variable onset after therapy initiation, are not dose-related, and are often reversible.

THERAPEUTIC VEGF INHIBITION

Classes of VEGF inhibitors act through different mechanisms to cause endothelial and glomerular injury. In the following section, we review the experimentally validated mechanisms by which VEGFA-VEGFR2 inhibitors contribute to nephrotoxicity.

ANTI-VEGF MAB

Pharmacologic agents that inhibit VEGFA activity through antibody binding include bevacizumab, ranibizumab, aflibercept, and ramucirumab. Bevacizumab and ranibizumab are mAbs against VEGFA and inhibit angiogenesis through IgG antibody interaction with all of its isoforms[31] (Figure 1i). Aflibercept, a recombinant fusion protein comprising binding domains for VEGFR1 and VEGFR2 attached to the Fc portion of human IgG1, acts as a soluble decoy receptor, or VEGF trap (Figure 1ii).[32] Ramucirumab, a fully humanized IgG1 mAb, specifically inhibits VEGFR2 by targeting its extracellular domain (Figure 1iii). Initial models of the first-in-class agent bevacizumab measured efficacy by reduced tumor growth using human breast cancer cell lines implanted into nude mice,[33] and the adverse outcomes of proteinuria and hypertension were not observed until phase 1 trials.[34] In murine models of direct VEGF inhibition in wild-type mice (Table 2), a single intravenous dose of anti-VEGF antibody produced significant albuminuria after 3 hours, as well as glomerular endothelial cell hypertrophy and disruption of glomerular basement membrane, seen by electron microscopy.[17] In validation of genetic knockout studies, mice given antibody directed at recombinant VEGF_{165} during the neonatal period (on days 0, 2, 4, and 5) displayed impaired glomerulogenesis, with poor cellularity and increased extracellular matrix deposition,[21] thereby confirming the essential role of VEGF signaling in glomerular development. Neither model showed lesions of TMA by histology, likely reflecting the short duration of treatment; however, the significant glomerular injury seen in both models underscores the importance of renal VEGF signaling during development as well as in homeostasis.

Findings from animal models demonstrate the importance of VEGF signaling during renal injury. In a rat model of crescentic GN, direct VEGF inhibition *via* an intramuscular injection of the soluble receptor for VEGFR1 (sFlt-1 plasmid), administered 3 days before injection of nephrotoxic serum, exacerbated crescent formation and albuminuria.[35] Similarly, subcutaneous injection of dRK6, which binds to VEGFA, worsened albuminuria and podocyte injury in *db/db* diabetic mice.[36] Both studies demonstrated the importance of VEGF signaling in maintaining glomerular integrity in disease as well as in homeostasis.

The nephrotoxicities associated with direct VEGF inhibition in patients receiving chemotherapeutics is primarily derived from clinical trial data (Table 3). In a meta-analysis of 20 phase 2 and phase 3 clinical trials involving bevacizumab-based therapy in solid tumors, the incidence of all-grade hypertension was 23.6% and high-grade (grade 3 or 4) hypertension was 7.9%.[37] Similarly, a meta-analysis of seven randomized, controlled trials (RCTs) found the incidence of proteinuria subsequent to bevacizumab therapy ranged from 21% to 62%, with the greatest risk associated with higher-dose therapy.[38] Data from six phase 2 trials showed that the incidence of all-grade hypertension and proteinuria after ramucirumab therapy for solid tumors was 21% and 9%, respectively.[39] A meta-analysis of 15 trials of aflibercept use in colorectal cancer found the incidence of all-grade and high-grade hypertension to be 42.4% and 17.4%, respectively; the risk of developing hypertension was significantly higher with aflibercept treatment compared with bevacizumab treatment.[40] Although some researchers have suggested that hypertension subsequent to VEGF inhibition is correlated with improved response to therapy,[41] a meta-analysis of seven phase 3 RCTs across multiple tumor types found no predictive significance of an early hypertensive response on clinical outcomes after bevacizumab treatment.[42] However, in patients receiving ramucirumab for gastric cancer, treatment-related hypertension was predictive of improved outcomes.[43,44]

Importantly, Eremina *et al.* reported that in a case series of six patients, bevacizumab use was associated with development of renal TMA. The patients had hypertension, proteinuria, and biopsy findings of glomerular endothelial cell injury (Table 3)—findings the investigators confirmed in a transgenic mouse model (Table 1).[8] This association was also noted in a large biopsy series, in which 66 out of 67 (98.5%) patients who received either bevacizumab or aflibercept had renal TMA; the remaining patient had FSGS.[9] Of those patients with biopsy-proven TMA, mean onset of disease was 6.9 months from the start of treatment; 83.5% had hypertension, and mean daily protein excretion was subnephrotic, at 2.5 g/d.[9] In contrast to the effects of systemic anti-VEGF therapy, intraocular anti-VEGF mAbs for the treatment of diabetic retinopathy typically has not been associated with these adverse effects.[45] However, there have been case reports of TMA with microangiopathic hemolytic anemia and thrombocytopenia after intravitreal ranibizumab,[46] and of onset of proteinuria and antibody-mediated rejection in kidney transplant patients after intravitreal bevacizumab, ranibizumab, and aflibercept.[47] In all, across multiple animal models, as well as in clinical trials, direct and systemic VEGF inhibition, *via* antibody binding or VEGF trap, results in hypertension, proteinuria, and a spectrum of glomerular endothelial injury.

Tyrosine Kinase Inhibitors of VEGF Signaling

Tyrosine kinase inhibitors (TKIs) inhibit RTKs, which consist of an extracellular binding domain, a transmembrane region, and an intracellular kinase that mediates signal transduction. TKIs interfere with the activity of one or more families of RTKs, including VEGFR, PDGF receptor (PDGFR), fibroblast growth factor receptor, and EGF receptor, which all share a similar structure. TKIs are thus commonly

Table 2. Renal manifestations from pharmacologic VEGF inhibition in murine models

Animal Model (Model/ Transgene, Strain, Age)	Drug	Mechanism	Target	Dose, Route and Frequency	Effects	Reference
Wild-type mice, CD1, age not specified	Anti-VEGF antibody and mouse sFlt-1/ Fc fusion protein (soluble VEGFR1)	Both treatments act to reduce circulating VEGF	VEGFA	3.25 and 32.5 pM, IV, single dose	Both treatments induced proteinuria by 3 h after administration, which resolved after 24 h. Both treatments resulted in GEnC hypertrophy and detachment from the basement membrane, starting at 3 h post-treatment and persisting to 24 h	17
Wild-type mice, strain not specified, neonatal	Antibody to recombinant human $VEGF_{165}$	Reduction of circulating VEGFA	VEGFA	100 μl/dose, IP, single dose on days 0, 2, 4, and 5 after birth	Decreased glomerular number and formation of abnormal glomeruli with poor cellularity and increased ECM. No significant changes in any nonglomerular vessels	21
Wistar Kyoto rats treated with antiglomerular basement membrane Ab, 12 wk	Mouse sFlt-1 plasmid	Soluble decoy receptor for VEGFR1. Reduction of circulating VEGFA	Soluble VEGFR1	500 μg, IM, 3 d before and 2 wk after injection of antiglomerular basement membrane Ab	Accelerated renal failure, proteinuria, interstitial fibrosis, endothelial cell loss. and downregulation of *Nephrin* in a model of rat crescentic GN	35
Wild-type mice, C57BL/6, 9–13 wk old	Axitinib (AG-013736)	Small molecule multitargeted TKI against VEGFR1–3, c-KIT, and PDGFR	VEGFR2, VEGFR1, VEGFR3, c-KIT, PDGFR	25 mg/kg, IP, twice daily for 7, 14 or 21 d For dose-response studies: 1, 10, or 100 mg/kg, oral gavage, twice daily for 7 d	Reduction in peritubular capillary density by 30% and glomerular capillary by 10% after 21 d of treatment. Dose dependent increase in proteinuria. Reduced glomerular capillary fenestrations. No increase in serum creatinine	51
Wild-type mice, C57BL/6, 9–13 wk old	Ad-sVEGFR1	Adenoviral vector that expresses the extracellular domain of murine VEGFR1. Acts as soluble decoy receptor for VEGF	Soluble VEGFR1	1×10^9 plaque-forming units, tail vein, once	No significant reduction in peritubular capillary or glomerular capillary density. Reduced glomerular capillary fenestrations and increase proteinuria after 14 d	51

Table 2. Continued

Animal Model (Model/ Transgene, Strain, Age)	Drug	Mechanism	Target	Dose, Route and Frequency	Effects	Reference
BALB/c$^{(Bicc1/Bicc1)}$ BPK model (murine phenocopy of ARPKD) and BALB/c wild-type controls, age not specified	Tesevatinib	TKI including EGFR, HER2/ErbB2, c-Src, and VEGFR2	VEGFR2, HER2, EGFR2, ERBB2	7.5 and 15 mg/kg, IP, daily postnatal day 4–21	Dose-dependent reduction in whole kidney size, total kidney weight; altered renal and liver morphology	48
PCK rat model (orthologous model of human ARPKD) and Sprague–Dawley wild type as control, age not specified	Tesevatinib	TKI including EGFR, HER2/ErbB2, c-Src, and VEGFR2	VEGFR2, HER2, EGFR2, ERBB2	7.5 and 15 mg/kg, oral gavage, daily for 60 d (from postnatal day 30–90)	Dose-dependent reduction in whole kidney size, total kidney weight; altered renal and liver morphology	48
UUO model and folic acid nephropathy models in male wild-type C57BL/6 mice, 6–8 wk	Nintedanib (BIBF11220)	A multitargeted TKI that blocks PDGFR, VEGFR, FGFR, and Src family kinases	PDGFR, VEGFR, FGFR, SRC	50 mg/kg, oral gavage, administered starting on day of UUO and then daily for 7 d	Attenuated renal fibrosis, inhibited activation of renal interstitial fibroblasts, and suppressed expression of proinflammatory cytokines after UUO	49
db/db and db/m male C57BL/6 mice, 6 wk	dRK6 (a D-amino acid derivative of RK6)	An arginine-rich anti-VEGF hexapeptide that binds with VEGF-A, and blocks the interaction between VEGFA (mainly $VEGF_{165}$ and $VEGF_{121}$) and the VEGFRs	VEGFA	50 μg, SC, three times per week starting at 8 wk of age and lasting until 12 wk (short-term) and 20 wk (long-term)	Both short-term and long-term treatment had decreased creatinine clearance compared with control *db/db* mice. Long-term treatment also exacerbated albuminuria, mesangial matrix expansion, and glomerulomegaly as compared with vehicle-treated *db/db* and short-term *dRK6*-treated *db/db* mice	36
Perinatal wild-type mice (exact age not specified)	DC101	mAb against the extracellular portion of the VEGFR2	VEGFR2	0.08 mg/dose, IP, on postnatal days 2 and 4	Large renal cysts, impaired glomerulogenesis (hypocellular), and increased albuminuria by 3 wk of age	50

Table 2. Continued

Animal Model (Model/ Transgene, Strain, Age)	Drug	Mechanism	Target	Dose, Route and Frequency	Effects	Reference
Male Wistar Kyoto rats 280–300 g, age not specified	Sunitinib	A multitargeted TKI including PDGFRα and PDGFRβ, VEGFR1, VEGFR2, and VEGFR3, and FMS-like tyrosine kinase-3	VEGFR1, VEGFR2, VEGFR3, PDGFRα, PDGFRβ, FMS-like tyrosine kinase-3	Low dose (7 mg/kg), intermediate (14 mg/kg) or high (26.7 mg/kg), oral gavage, once daily for 8 d	All doses associated with hypertension and proteinuria. Intermediate and high doses were associated with endothelial swelling. High-dose only was associated with fibrin deposits in glomerular capillaries and small arteries	52

IV, intravenous; GEnC, glomerular endothelial cells; IP, intraperitoneal; ECM, extracellular matrix; Ab, antibody; IM, intramuscular; c-KIT, tyrosine-protein kinase Kit; PDGFR, PDGFR receptor; ARPKD, autosomal-recessive polycystic kidney disease; PCK, polycystic kidney; UUO, unilateral ureteric obstruction; EGFR, EGF receptor; FGFR, fibroblast growth factor receptor; SC, subcutaneous.

called multitargeted TKIs, and have different effects depending on their specificity. TKIs targeting VEGFR in clinical use as chemotherapeutics include sunitinib, pazopanib, sorafenib, and axitinib, and differ because of their distinctive pharmacodynamic properties (Figure 1iv).

The varying effects of TKIs in various murine models that have used these agents across a spectrum of kidney diseases reflect the wide range of action and targets of TKIs (Table 2). In the *bpk* mouse model for autosomal recessive PKD, intraperitoneal injection of tesevatinib (a multikinase inhibitor targeting EGF receptor, HER2, and VEGFR) from postnatal days 4–21 attenuated cyst formation in the kidney and liver and reduced total kidney weight.[48] Treatment with the multitargeted TKI nintedanib attenuated renal fibrosis in wild-type mice subjected to unilateral ureteral obstruction and folic acid nephropathy.[49] In contrast to the renal benefit seen with multitargeted TKIs, inhibition of VEGFR2 alone with an antibody resulted in spontaneous renal cyst development when given perinatally in mice,[50] and giving 10-week-old mice axitinib (a TKI targeting primarily VEFGR1, VEGFR2, and VEGFR3) resulted in loss of glomerular capillary fenestrations as well as proteinuria.[51] Similarly, Wistar Kyoto rats given sunitinib, which mainly targets PDGF and VEGF receptors, exhibited proteinuria, hypertension, and endothelial injury.[52]

A review of 72 RCTs using TKIs targeting VEGFR1/VEGFR2 found that these drugs, like monoclonal anti-VEGF antibody therapies, were associated with an increased risk of hypertension. Among patients receiving the TKIs, the total incidence of all-grade or high-grade hypertension was 23.0% and 4.4%, respectively; sunitinib, pazopanib, cabozantinib, vandetanib, motesanib, regorafenib, cediranib, and sorafenib were associated with the highest risk.[53] A separate study involving 1120 patients treated with TKIs observed a rapid and significant increase in systolic and diastolic BP after initiation of therapy, with a median onset of 29 days after first dose. Risk factors for treatment-induced hypertension in that cohort were preexisting hypertension, body mass index >25, and age >60 years.[54] Similarly, the incidence of all-grade and high-grade

Table 3. Clinical manifestations of VEGF inhibition

Drug[a]	Class	Renal Manifestations (Level of Evidence)	References
Bevacizumab	mAb against VEGFA	Proteinuria 21%–62% (level 1), all-grade[b] hypertension 23.6% and high-grade[c] hypertension 7.9% (level 1), renal TMA (levels 6 and 7), MCD/cFSGS-like glomerulopathy (level 6), ABMR-intraocular (level 7)	8,9,34,37,38
Ranibizumab (intraocular)	mAb against VEGFA	Systemic and renal TMA (level 7), proteinuria (level 7), ABMR-intraocular (level 7)	46,47
Aflibercept	Recombinant fusion protein	All-grade[b] hypertension 42.4% and high-grade[c] hypertension 17.4% (level 1), proteinuria, TMA (level 6), ABMR-intraocular (level 7)	9,40
Ramucirumab	mAb against VEGFR2	All-grade[b] hypertension 21% (level 1), proteinuria 9% (level 1)	39
Sunitinib	Multitargeted TKI	All-grade[b] hypertension 14.9% (level 1), MCD/cFSGS-like glomerulopathy (level 6), nephrotic syndrome (level 7)	9,53,56
Pazopanib	Multitargeted TKI	All-grade[b] hypertension 47% (level 1), all-grade[d] proteinuria 13.5% and high-grade proteinuria 2.2% (level 1)	53,55
Sorafenib	Multitargeted TKI	All-grade[b] hypertension 18.1% (level 1), MCD/cFSGS-like glomerulopathy (level 6), TMA (level 6), all-grade[d] proteinuria 11.6% and high-grade[e] proteinuria 0.9% (level 1)	9,53,55
Cabozantinib	Multitargeted TKI	All-grade[b] hypertension 32.7% (level 1)	53
Vandetanib	Multitargeted TKI	All-grade[b] hypertension 17.3% (level 1), all-grade[d] proteinuria 10.0% and high-grade[e] proteinuria 0% (level 2)	53,55
Motesanib	Multitargeted TKI	All-grade[b] hypertension 26.1% (level 1)	53
Cediranib	Multitargeted TKI	All-grade[b] hypertension 42.5% (level 1), all-grade[d] proteinuria 37.8% and high-grade[e] proteinuria 3.9% (level 1)	53,55
Axitinib	Multitargeted TKI	All-grade[b] hypertension 27.1% (level 1), all-grade[d] proteinuria 20.2% and high-grade[e] proteinuria 4.6% (level 1)	53,55
Regorafenib	Multitargeted TKI	All-grade[b] hypertension 32.4% (level 1), all-grade[d] proteinuria 7.0% and high-grade[e] proteinuria 1.4% (level 2)	53,55
Tivozanib	Multitargeted TKI	All-grade[d] proteinuria 9.6% and high-grade[e] proteinuria 1.5% (level 1)	55
Linifanib	Multitargeted TKI	All-grade[d] proteinuria 27.3% and high-grade[e] proteinuria 6.8% (level 1)	55
Dasatinib	Multitargeted TKI	Nephrotic syndrome (level 7)	56
Imatinib	Multitargeted TKI	Nephrotic syndrome (level 7)	56
Quizartinib	Multitargeted TKI	Nephrotic syndrome (level 7)	56
Vemurafenib	BRAF inhibitor	AKI, acute tubular necrosis (level 7)	73
Dabrafenib	BRAF inhibitor	Nephrotic syndrome with severe podocyte and endothelial cell injury when used in combination with trametinib (level 7)	26
Trametinib	MEK inhibitor	Nephrotic syndrome with severe podocyte and endothelial cell injury when used in combination with dabrafenib (level 7)	26

Levels of evidence: level 1: systematic review or meta-analysis of RCTs; level 2: one well designed RCT; level 3: one controlled trial without randomization; level 4: case–control or cohort studies; level 5: systematic review of descriptive and qualitative studies; level 6: one descriptive or qualitative study; level 7: case series or case report. MCD/cFSGS-like, minimal change disease and/or collapsing FSGS; ABMR, Antibody Medicated Rejection.

[a] All drug delivery routes are systemic unless otherwise specified.

[b] All-grade hypertension: grades 1–4. Grade 1: asymptomatic transient increase in systolic BP/diastolic BP >20 mm Hg or <150/100 not requiring therapy; grade 2: recurrent or persistent or symptomatic increase in systolic BP/diastolic BP >20 mm Hg or >150/100, not requiring therapy; grade 3: 4equires therapy or more intensive therapy than previous; grade 4: hypertensive crisis.

[c] High-grade hypertension: combined grades 3 and 4.

[d] All-grade proteinuria: grades 1–5 (National Cancer Institute toxicity grading criteria version 2 and 3 for proteinuria). Grade 1: dipstick 1+ or 0.15–1.0 g/24 h; grade 2: dipstick 2+ to 3+ or 1.0–3.5 g/24 h; grade 3: dipstick 4+ or >3.5 g/24 h; grade 4: nephrotic syndrome; grade 5: death.

[e] High-grade proteinuria: grades 3–5.

proteinuria across 33 clinical trials of patients with solid tumors treated with VEGFR TKIs was 18.7% and 2.4%, respectively.[55]

In contrast to renal biopsy specimens from patients treated with anti-VEGF mAbs or VEGF trap, biopsy specimens for the majority of the patients receiving TKIs exhibited podocytopathies, including minimal change disease (MCD) and collapsing FSGS[9] (Figure 2). In addition, a case series of four pediatric patients presented by Ruebner *et al.* reported that the administration of TKIs (imatinib, dasatinib, quizartinib, and sunitinib) produced severe nephrotic syndrome with marked albuminuria, edema, and decreased serum albumin. Although full evaluation was limited by a lack of biopsy in three of the patients, the biopsy sample from the fourth patient showed histology and electron microscopy findings were consistent with MCD[56]; another patient had laboratory evidence consistent with TMA in addition to nephrotic syndrome.[56]

Some evidence suggests that the increase in podocyte injury subsequent to TKIs might be mediated by tyrosine phosphorylation of

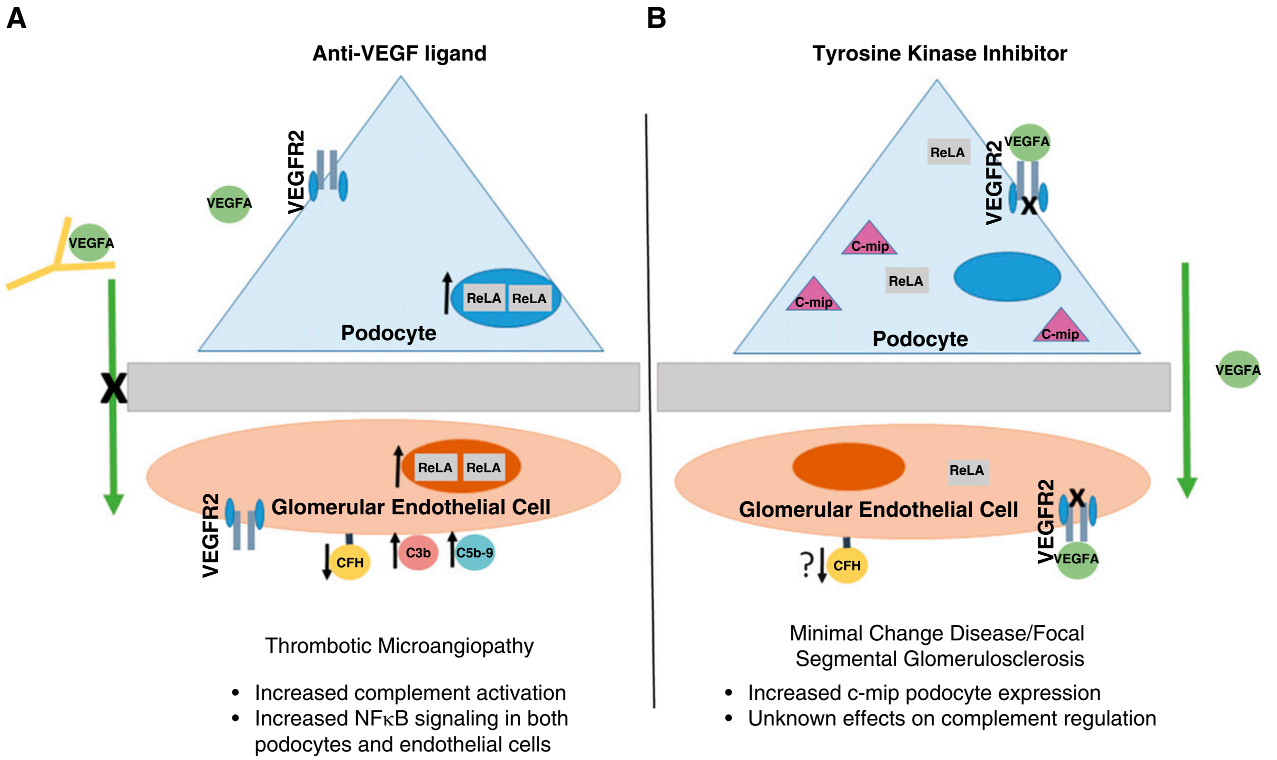

Figure 2. Inhibition of VEGFA-VEGFR2 signaling has differential downstream effects, depending on the therapeutic target. (A) During treatment with anti-VEGF ligand, podocyte secreted VEGFA is sequestered and does not bind to either podocyte or endothelial VEGFR2 (large X). This leads to increased NF-κB signaling and RelA translocation to the nucleus in both glomerular endothelial cells as well as podocytes. CFH is downregulated on glomerular endothelial cells, which leads to increased complement activation. (B) Treatment with TKIs allows VEGFA to bind to glomerular endothelial and podocyte VEGFR2, but inhibits downstream signaling (small x's). This induces RelA retention in the cytoplasm and c-mip overexpression in the podocyte, leading to alterations in the cytoskeleton and nephrotic syndrome. The effects of TKIs on complement activation remain unclear.

nephrin. Simons *et al.*[57] showed that tyrosine phosphorylation of nephrin, an essential slit-diaphragm protein in podocytes, is critical to maintain the integrity of the filtration barrier. This was demonstrated in a murine model, in which an injection of antibody against nephrin-containing lipid rafts caused effacement of podocyte foot processes.[57] Furthermore, New *et al.*[58] demonstrated in a knock-in murine model that blocked tyrosine phosphorylation of nephrin that the mice developed proteinuria with podocyte effacement, emphasizing the importance of direct nephrin phosphorylation on the maintenance of podocyte morphology.[59,60] Interestingly, administration of the TKI sunitinib for eight consecutive days in normotensive Wistar Kyoto rats resulted in a dose-dependent decrease in expression of *Nephrin* mRNA; however, protein levels or phosphorylation status were not quantified.[52] Further, in another study, induction of podocyte-specific overexpression of *Vegfa*$_{164}$ in transgenic mice not only resulted in expression of VEGFR2 protein in podocytes, but the VEGFR2 was also tyrosine phosphorylated and colocalized with nephrin, effects not seen in wild-type mice.[28] In the same study, the researchers used whole kidney lysates to coimmunoprecipitate VEGFR2 and nephrin, demonstrating that the two physically interact *in vivo*. This suggests that when VEGFA availability increases, VEGFR2 is expressed in podocytes in addition to endothelial cells, and can be phosphorylated by podocyte-derived VEGFA.[28] These changes were associated with glomerulomegaly, mesangial expansion, basement membrane thickening, and foot process effacement.[28]

Molecular studies of biopsied kidney samples from 29 patients with solid tumors after they were treated with either a TKI (sunitinib, axitinib, or sorafenib) or a direct anti-VEGF therapy (bevacizumab or VEGF trap) also attempted to elucidate mechanisms behind the two distinct patterns of glomerular injury, TMA and MCD/FSGS, after VEGF inhibition (Figure 2).[61] Immunostaining revealed that MCD/FSGS lesions are associated with increased glomerular C-Maf–inducing protein (c-mip), which was not seen in TMA patients. In TMA biopsy specimens but not in MCD/FSGS biopsy specimens, glomerular RelA, a subunit of the transcription factor NF-κB, was significantly upregulated, reflecting increased NF-κB activity.[61] The authors showed that the massively upregulated RelA seen in TMA directly suppresses c-mip activity by binding to its promotor.[61] This association of c-mip overexpression and direct podocyte injury has been characterized previously in human, murine, and *in vitro* studies.[62]

In all, the diverse renal effects of the various TKIs can be ascribed to their multitargeted design. Specific mechanisms of direct podocyte injury after treatment with TKIs can be attributed to modulation of NF-κB activity and c-mip expression, as well as nephrin phosphorylation and interaction with VEGFR2, but require validation in future studies.

VEGF SIGNALING PATHWAYS

To get a full picture of the nephrotoxicity associated with inhibition of VEGF signaling, it is critical to gain an understanding of the downstream mechanisms and regulatory cascades initiated by VEGFR2 activation. Key downstream signaling pathways include MAPK/ERK1/2, endothelial nitric oxide synthase (eNOS), and mammalian target of rapamycin (mTOR).

RAF/MAPK/ERK SIGNALING

One pathway that has been extensively studied is VEGF-induced ERK1/2 signaling, which serves to regulate endothelial differentiation and proliferation.[63] In the kidney, MAPK/ERK signaling has diverse effects. Parietal epithelial cells in experimental FSGS[64] show increased ERK1/2 activation, and it is also associated with increased podocyte apoptosis in diabetic conditions.[65] In contrast to its association with pathologic consequences in renal epithelial cells, in glomerular endothelial cells, MAPK/ERK signaling is required for the protective effects of angiopoietin 1 against endoplasmic reticulum stress.[66] In cultured glomerular endothelial cells, ERK1/2 inhibition completely suppressed VEGF-mediated proliferation, but migration was not affected.[67]

Outside of the kidney, VEGF induces ERK1/2 phosphorylation in a time- and concentration-dependent manner and is responsible for its effects on endothelial cell hyperpermeability.[20] This VEGF-mediated ERK1/2 signaling is dependent on the upstream mediators Raf-1 and MEK, as inhibition of either attenuated VEGF-induced endothelial cell hyperpermeability.[20]

In addition, Takahashi *et al.* showed the importance of the VEGFR2/MAPK/ERK downstream pathway in cultured endothelial cells by determining that Y1175 is the major VEGFA-dependent autophosphorylation site on VEGFR2. Furthermore, mutations introduced at the Y1175 phosphorylation domain on VEGFR2 resulted in loss of the ability to tyrosine phosphorylate phospholipase C-γ, as well as a significant reduction in MAPK phosphorylation and a corresponding reduction in DNA synthesis. These effects suggest that Y1175 plays a critical role in MAPK signal transduction.[68]

The importance of autophosphorylation of VEGFR2 was also subsequently demonstrated by Sakurai *et al.*[69] who used a constitutive knock-in mouse model with phenylalanine residues substituting for tyrosine residues in the *Vegfr2* gene—a change that was embryonically lethal because of loss of blood vessel differentiation. Furthermore, the critical nature of VEGF-ERK signaling was underscored in a study of a cohort of patients with hepatocellular carcinoma that found that tumors with highest expression of phospho-ERK were more responsive to VEGF inhibition *via* TKI.[70]

Therapeutic inhibitors that target various portions of the MAPK/ERK are currently in development as novel chemotherapies. Some agents, such as vemurafenib and dabrafenib, specifically target B-Raf, an upstream component of the intracellular MAPK/ERK intracellular pathway (Figure 1v). Mutated B-Raf, as is found in various cancers,[71] results in persistently elevated ERK phosphorylation. Clinically apparent renal toxicity with the use of B-Raf inhibitors most often occurs in the tubulointerstitial compartment, manifests as AKI, and is more prevalent in males, according to a recent review (Table 3).[72] Specifically, vemurafenib treatment in eight patients with malignant melanoma resulted in severe AKI; the single biopsy performed revealed acute tubular necrosis.[73] Interestingly, treatment with the combination of dabrafenib and the MEK inhibitor trametinib resulted in severe nephrotic syndrome with podocyte effacement and glomerular endothelial cell injury on biopsy that was reversible upon therapy discontinuation.[26] Direct ERK1/2 inhibitors are also in development. A recently completed phase 1 trial of the first of these agents to emerge from preclinical studies, ulixertinib, noted that no adverse renal events have emerged so far.[74] Still, the potential nephrotoxicity associated with the inhibition of key proteins in the RAS-RAF-MEK-MAPK-ERK1/2 pathway demonstrates a need to further explore downstream effectors of extracellular receptor activation that are specific to the tumor, as well as minimize nephrotoxicity.

ENOS SIGNALING

Some investigators have postulated a reduction in the vasodilator eNOS as a potential mechanism underlying the hypertension and endothelial injury seen subsequent to pharmacologic VEGF inhibition. Mice with eNOS deficiency (*Nos3*$^{-/-}$) exhibit endothelial injury in the form of increased platelet aggregation,[75] leukocyte adhesion,[76] propensity toward thrombosis,[76] and hypertension.[77] Downstream of VEGFA-VEGFR2 signaling in human umbilical vein cells[78] and glomerular endothelial cells, phosphorylation of eNOS at Ser1177 induces eNOS in a time-dependent manner, leading to nitric oxide generation.[79] Furthermore, the angiogenic effects of VEGF-VEGFR2 are mitigated in the absence of eNOS.[80,81] Evidence supporting the role of VEGF in the hypertensive response comes from Tang *et al.*[82] who found that a single dose of the selective VEGFR2 inhibitor SU5416 significantly downregulated lung eNOS expression in 3-day-old rats and induced pulmonary hypertension and right ventricular hypertrophy; these effects were attenuated with inhaled nitric oxide therapy. There are reports of the TKIs dasatinib and ponatinib inducing pulmonary arterial hypertension after their use in patients,[83] and ponatinib administered to cultured human aortic endothelial cells has been similarly associated with decreased *NOS3* expression.[84]

In light of eNOS's essential role of in regulating vascular endothelial integrity through VEGF signaling, it is important to consider the contribution of other key endothelial regulatory genes in this pathway. Krüppel-like factor 2 (KLF2) and Krüppel-like factor 4 (KLF4) are well known zinc-finger transcription factors that regulate anti-inflammatory[85,86] and antithrombotic[87] pathways in the endothelium.

KLF2 induces both eNOS expression and activity in endothelial cells by regulating its promoter,[88] and KLF4 has also been demonstrated to positively regulate eNOS expression.[89] Interestingly, these two transcription factors appear to have discrepant effects on VEGFA-VEGFR2 signaling: *KLF2* overexpression in human umbilical vein cells inhibited VEGFR2 mRNA and protein expression, as well as promoter activity, suggesting an antiangiogenic effect,[90] whereas KLF4 has been demonstrated to positively regulate VEGFA expression.[91] Further exploration of these signaling pathways is warranted to elucidate the mechanisms by which VEGF inhibition contributes to the nephrotoxicity observed in clinical practice.

MTOR SIGNALING

Another important downstream RTK target, mTOR, is part of the phosphatidylinositide 3-kinase/AKT signal transduction pathway (Figure 1vi). Inhibition of mTOR signaling blocks VEGF-mediated angiogenesis and endothelial cell proliferation at two different levels: by reducing VEGF synthesis and secretion, and by reducing VEGFR2-mediated signaling.[92] The mechanism responsible for the decreased VEGF production is not fully understood, but it does not appear to be due to modulation of upstream genes such as HIF-1α or TGF-β.[92] Activation of mTOR occurs in conditions such as tuberous sclerosis and Peutz–Jeghers syndrome, which feature aberrant cell proliferation and a tendency to develop malignancies,[93] and mTOR inhibitors such as temsirolimus, ridaforolimus, and everolimus have shown promising results in the treatment of several cancers.[94]

In the kidney, several studies have outlined the importance of mTOR in the maintenance of podocyte integrity, primarily through regulation of autophagy,[95] as deletion of either of its two functional complexes (mTOR complex 1 or mTOR complex 2) resulted in severe glomerulosclerosis.[96] Although mTOR's role in podocytes has been more extensively studied, the mTOR autophagic pathway has a role in endothelial cells as well. The finding that endothelial-specific knockdown of *Atg5*, which encodes a key autophagic vesicle protein, exacerbated glomerular endothelial damage in diabetic mice[97] suggests that modulation of the mTOR pathway in endothelial cells may also result in glomerular disease.

Proteinuria is the main renal effect subsequent to mTOR downregulation in murine models of podocyte injury, as well as the primary renal manifestation observed in patients after mTOR inhibition. The reported incidence of proteinuria varies widely, between 3% and 36% after everolimus therapy.[98] Interestingly, the mTOR inhibitor sirolimus has been associated with *de novo* TMA in kidney transplant recipients that developed in the absence of calcineurin inhibitors, and in one case series, sirolimus correlated with a significant reduction in glomerular VEGF protein expression detected by immunostaining.[99] This observation was explored further in a murine model, in which mice with podocyte-specific deletion of *mTor* developed significant proteinuria and ESRD by 5 weeks of age.[100] In this model, VEGFA levels were not reduced until the mice were 3 weeks old, after the initiation of disease, suggesting multiple pathways are likely responsible for disease induction and progression.[100] Accordingly, the mechanisms behind renal toxicities related to mTOR inhibition have been postulated to be related to a decrease in VEGF signaling, as well as to disruption of the autophagic pathway.[100]

CLINICAL CONSIDERATIONS FOR MINIMIZING NEPHROTOXICITY

Managing the various renal toxicities associated with VEGF inhibition will remain an important area of ongoing research because of the wide use of these agents and the steady development of novel therapeutics targeting this pathway in cancer. Experimental data from rats treated for 5 days with the TKI sunitinib demonstrated that coadministration of sunitinib with either the angiotensin-converting enzyme (ACE) inhibitor captopril or the phosphodiesterase type 5 inhibitor sildenafil reduced proteinuria and histologic evidence of endothelial injury, whereas neither had an effect on sunitinib-induced hypertension.[101] The mechanism behind these renoprotective effects is undetermined, but it might involve eNOS signaling, as both ACE inhibitors and angiotensin receptor blockers have been shown to increase kidney eNOS levels after ischemia-reperfusion injury.[102]

Guidelines published in 2010, on the basis of recommendations to that National Cancer Institute's Investigational Drug Steering Committee, advise conducting and documenting a formal risk assessment of cardiovascular complications before initiation of VEGF inhibition, followed by active BP monitoring during VEGF inhibition therapy, with a treatment goal of BP $<140/90$ mm Hg.[103] The addition of antihypertensive agents when BP remains above goal is recommended, with some clinical data suggesting an added benefit of ACE inhibition over other classes.[104] Temporarily discontinuing VEGF inhibition therapy or dose reduction might be necessary if BP control is not possible.[103]

Microalbuminuria often accompanies hypertension,[38] and first-line therapy is generally renin-angiotensin-aldosterone system inhibition, as this has shown some success in mTOR antagonist–associated albuminuria after kidney transplantation.[105] Albuminuria should be quantified before initiating therapy, and significant proteinuria (>2 g in 24 hours) is cause for discontinuation of therapy per 2013 guidelines,[106] as is nephrotic syndrome or TMA. In the cases of nephrotic-range albuminuria, hematuria, or biochemical evidence of impaired kidney function, kidney biopsy should be pursued, as glomerular diseases associated with VEGF inhibition vary. In all, close monitoring during therapy and a thorough assessment of renal function before initiation, including microalbuminuria, hematuria, and serum creatinine, should be performed in all patients receiving VEGF inhibition therapy.

CONCLUSIONS AND FUTURE PERSPECTIVES

Pharmacologic inhibition of VEGF signaling and its downstream pathways is a common therapeutic strategy in oncology, but associated nephrotoxicities remain a concern. Although adverse effects such as hypertension, proteinuria, and TMA are well described in both experimental and clinical data, strategies to mitigate them have not been established. Furthermore, long-term data are lacking regarding the effects of VEGF inhibition and risk of subsequent CKD or hypertension. Given increasing survival among patients with cancer who receive anti-VEGF therapy, this is an important area to investigate, as is identification of novel mechanisms to reduce nephrotoxicities of VEGF-inhibiting drugs without compromising the drugs' antiangiogenic effects in cancer.

ACKNOWLEDGMENTS

This work was supported by funds from the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases (grants DK102519 and DK112984 to S.K.M., and grant DK112618 to C.C.E.), Veterans Affairs Merit award (1I01BX003698) to S.K.M., and Dialysis Clinic, Inc. (Paul Teschan research grant) to C.C.E. and S.K.M.

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DISCLOSURES

None.

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