Nephrotoxicity induced by vascular endothelial growth factor inhibitors

Shirinsadat Badri[1] , Lillian Siberian[2] , Rasool Soltani[3] , Azadeh Moghaddas[3] , Sara Ataei[4] ,
Mahnaz Momenzadeh[3*]

[1]Department of Clinical Pharmacy and Pharmacy Practice; Isfahan Kidney Diseases Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Independent Researcher and Author, Toronto, Ontario, Canada
[3]Department of Clinical Pharmacy and Pharmacy Practice, School of Pharmacy and Pharmaceutical Sciences; Infectious Diseases and Tropical Medicine Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[4]Department of Clinical Pharmacy, School of Pharmacy, Hamadan University of Medical Sciences, Hamadan, Iran

ABSTRACT

Vascular endothelial growth factor (VEGF) is a special mitogen for vascular endothelial cells, an essential endogenous angiogenic cytokine, and the principal controller of vascular growth that plays a fundamental role in therapeutic angiogenesis pathways. VEGF-targeted therapy is categorized into the group of angiogenesis inhibitors that inhibit the expression or the activity of VEGF. It comprises counteracting VEGF antibodies, VEGF receptors, VEGF-trap, and tyrosine kinase inhibitor (TKIs) with selectivity for VEGF receptors. The kidney is both a target and a source of VEGF. VEGF may be a vital mediator to restore some types of renal diseases (e.g., non-diabetic renal diseases) and harmful in some other diseases (e.g., diabetes and diabetes complications). Due to their ability to prevent angiogenesis, VEGF inhibitors have been found as a powerful tool to treat angiogenesis-dependent diseases, including cancer and diabetic retinopathy. VEGF preserves the renal structure and function in normal physiologic conditions. Therefore, all treatments that inhibit the VEGF pathway may lead to renal disorders, especially renovascular diseases such as hypertension, proteinuria, nephrotic syndrome, decreased glomerular filtration rate (GFR), and thrombotic microangiopathy (TMA). In the present study, we reviewed some related reports and associated mechanisms, especially for hypertension and proteinuria.

Introduction

Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) is a special mitogen for vascular endothelial cells, an essential endogenous angiogenic cytokine, and the primary controller of vascular growth that plays a fundamental role in therapeutic angiogenesis pathways. It promotes endothelial cell proliferation, differentiation, and survival. VEGF also resolves endothelium-dependent vasodilatation and promotes microvascular permeability. Recent studies have shown the pathological role of VEGF in developing severe microvascular and morphologic variations in different renal diseases, including chronic kidney disease (CKD), acute kidney injury (AKI), diabetic nephropathy, atherosclerosis, and metabolic syndrome (1).

The human VEGF family comprises VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor. VEGF-A, the most significant member of this family, is initially recognized as a vascular permeability factor, which regulates blood vessel growth in physiological and pathological angiogenesis (2). VEGF-targeted therapy is categorized into the group of angiogenesis inhibitors that inhibit VEGF activity. It comprises anti-VEGF antibodies (e.g., bevacizumab), VEGF receptor antagonist (ramucirumab), VEGF soluble receptor (e.g., aflibercept),

Corresponding author: Mahnaz Momenzadeh, Email: Mahnazmomenzadehf@gmail.com, Mahnaz.momenzadeh@pharm.mui.ac.ir

and tyrosine kinase inhibitors (TKIs) with selectivity for VEGF receptors (e.g., sunitinib and sorafenib) (3). For instance, bevacizumab, a monoclonal antibody, counteracts VEGF after its release from tumor cells, while sunitinib, a multiple receptor TKI, prevents endothelial cell receptors, inhibiting their response to the released VEGF. Ranibizumab, a monoclonal antibody, is a shorter-acting agent with comparable potency to bevacizumab. Aflibercept, however, is a more potent and longer-acting VEGF-Trap compared with bevacizumab. Pegaptanib is the first ribonucleic acid aptamer, another class of VEGF-binding molecules (4).

Method of the study

Relevant articles published were searched in PubMed/ Medline, Scopus and Embase. The following search terms such as "thrombotic microangiopathy, glomerular filtration rate, vascular endothelial growth factor, chronic kidney disease and angiogenesis", were employed to retrieve the published articles on this subject.

Kidney role and VEGF

The kidney is both a target and a source of VEGF. Tubular epithelial cells and podocytes are the primary renal VEGF sources, while the main targets of VEGF in the kidney are endothelial cells and podocytes. The kidney receives a significant proportion of blood flow through glomerular and peritubular microvasculature since VEGF plays a central role in the growth and proliferation of this vascular network. It is also essential for both the metabolic demands of the kidney and whole-body homeostasis, such as blood pressure, body fluid, pH, and electrolyte balance (1,5).

VEGF may be a vital mediator of restoring some renal diseases and harmful in some other diseases (1,6). Some studies have discovered that VEGF therapy decreases renal diseases and stabilizes renal function in CKD models (7,8). In various non-diabetic renal diseases, VEGF plays nephroprotective roles, improves renal function, and decreases renal fibrosis. It suggests that VEGF inhibition is harmful to podocyte and renal function and is associated with the development of glomerulosclerosis and tubulointerstitial fibrosis in the remnant kidney. Therefore, the pathophysiologic role of VEGF and its therapeutic application for the kidney have been supported.

However, VEGF shows deleterious roles in the pathophysiology of diabetes and diabetes complications through mediating the development/progression of diabetic nephropathy. Therefore, the inhibition of VEGF has beneficial effects on diabetes-induced functional and structural changes in the kidney (7).

Anti-VEGF

Angiogenesis is characterized by the imbalance of several pro- and anti-angiogenic factors. Among several pro-angiogenic factors, VEGF is recognized as the best regulator of angiogenesis, both in health and disease, which is the crucial target for the therapeutic stimulation of vascular growth. Anti-angiogenic treatment is an original and efficient pathway for the treatment of angiogenesis-dependent diseases. Due to their ability to prevent angiogenesis, VEGF inhibitors have advanced as powerful tools to treat angiogenesis-dependent diseases, such as cancer and diabetic retinopathy.

Anti-VEGF and cancer

Angiogenesis holds a primary role in tumor growth and metastasis. It provides an essential supply of oxygen and nutrients for tumor growth and promotes the detachment of primary tumor cells from the general circulation, resulting in the spread of cancer. In cancer, VEGF is released by tumor cells, fibroblasts, and inflammatory cells into the tumor stroma. It generally modulates tumor growth, recurrence, invasiveness, and metastasis of tumor cells (9). Therefore, anti-VEGF agents have been considered as anti-cancer agents in recent years (2).

Angiogenesis could be a factor in the progression of polycystic kidney disease (PKD). Although PKD-induced neovascularization leads to a disordered vascular network, relevant studies demonstrated that anti-angiogenic treatments in PKD through VEGF inhibition did not improve the disease and may have even led to cyst development and end-stage renal disease (ESRD) in some conditions (10).

Anti-VEGF and ocular diseases

The usual expression of VEGF causes preserving the structural and functional homeostasis of the retinal cells, while VEGF overexpression could result in retinal angiogenesis due to pathological conditions, including hypoxia and hyperglycemia (11). Clinical studies exhibited significant vitreous and circulating VEGF overexpression in the serum of patients with type 1 and type 2 diabetes, diabetic retinopathy and nephropathy.

There might be a correlation between VEGF production and hypoxia-induced neovascularization in the eye, which may result in a more vigorous neovascular response (12). Therefore, serum VEGF level, specifically VEGF-A, is suggested as a reliable biomarker for assessing the development and progression of diabetic retinopathy (13).

VEGF inhibitors have improved the treatment control of numerous retinal ophthalmic diseases, such as proliferative diabetic retinopathy, central retinal vein occlusion, diabetic macular edema, and age-related macular degeneration (14).

Shye et al reviewed 23 published case reports of deteriorating renal function and hypertension following intravitreal VEGF blockade (15). These studies recommended a crucial requirement for

earlier investigations of long-term VEGF inhibition's pathological effects with intra-vitreal injections due to significantly lower consumption (almost 400 times lower) and lower toxicity. Intravitreal VEGF inhibition risks can be estimated at almost 14% for hypertension deterioration and 14–45% for proteinuria deterioration. The risks of intravitreal VEGF inhibition are lower than systemic VEGF inhibition, in which 21–63% of patients show deteriorating proteinuria and 24% have deteriorating hypertension (15).

Nephrotoxic effects of VEGF and its mechanisms

Despite all developments in anti-VEGF drugs, a key challenge for the clinical administration of these treatments is the adverse effects of these treatments on healthy tissues (16). VEGF preserves the renal structure and function in normal physiologic conditions. Thus, all treatments inhibiting the VEGF pathway may lead to kidney disorders that are mainly renovascular diseases involving proteinuria, hypertension, nephrotic syndrome, decreased glomerular filtration rate (GFR), and thrombotic microangiopathy (TMA) (3,17).

There are various reported cases of renal TMA, increased proteinuria, and antibody-mediated renal allograft rejection after the intravenous administration of high doses of VEGF inhibitors (18-20).

Hypertension

There are numerous mechanisms whereby anti-VEGF agents may result in hypertension. The inhibition of VEGF decreases the expression of endothelial nitric oxide synthase, and consequently, lowers nitric oxide production. Reduced nitric oxide lead to elevation of blood pressure through the increase of vasoconstriction and sodium retention. In addition, the VEGF pathway's inhibition can result in hypertension by microvascular rarefaction, and consequently, cause an increase in peripheral resistance, fibrosis, and deficit of podocytes (21). Increased oxidative stress can cause endothelial damage and hypertension, while VEGF prevents the endothelial damage induced by oxidative stress (22).

Proteinuria

Following VEGF signaling inhibition, the increased loss of proteins in urine (proteinuria) is a dose-dependent adverse effect and may indicate a severe glomerular injury. The inhibition of the VEGF signaling axis prompts the reduction or elimination of nephrin, a vital protein for conserving the glomerular filtration barrier that may cause nephritic syndrome or glomerular TMA. The pathogenesis of proteinuria in patients receiving anti-VEGF therapy is probably associated with numerous alterations, such as the perturbation of podocyte-endothelial VEGF axis signaling, post-exercise proteinuria-like syndrome, podocyte protein junction down-regulation, and subacute

glomerular TMA.

The exact mechanism of proteinuria exacerbated by drugs targeting VEGF is not well understood; however, several theories have been suggested. First, the imbalance of VEGF-A expression (e.g. bevacizumab) would lead to structural and functional changes in the glomerular cells. Second, loss of selective glomerular permeability may occur due to the damage of glomerular filtration barrier and increase of glomerulosclerosis (23). Other mechanisms involve reduced nitric oxide bioavailability, renal damage, and increased intra-glomerular pressure induced by arterial hypertension (24). There is an association between proteinuria and hypertension after VEGF inhibition; however, it is unclear whether hypertension causes proteinuria or vice versa or they are independent of each other.

VEGF blockade in experimental glomerulonephritis does not lead to proteinuria. Conversely, the podocyte-specific overexpression of VEGF induces a collapsing glomerulopathy instead of a simple proteinuria. Regular checking of urinary protein in patients treated with anti-VEGF drugs is necessary, and those displaying nephrotoxicity require referral to a nephrologist (25).

While there is limited information concerning kidney biopsies in patients treated with anti-VEGF, studies have confirmed the presence of focal segmental glomerulosclerosis (FSGS) and TMA. There are also limited reports of nephritic syndrome, AKI, IgA nephropathy, preeclampsia-like syndrome, acute interstitial nephritis, and cryoglobulinemia due to anti-VEGF therapy (3,26).

The recent prospective management of anti-angiogenics' renovascular safety study (MARS) on 1126 patients treated with the anti-VEGF drug bevacizumab for the first time, especially in ovarian (27), lung (28) and breast (29) cancers, reported no case of TMA. Notably, the MARS study confirmed that baseline hypertension could be a risk factor and potential biomarker of activity/efficacy for patients with reduced GFR treated with anti-VEGF drug therapy (30), particularly for anti-VEGF-TKIs.

Previously, Izzedine et al studied 100 cancer patients with an average age of 60 years administrated anti-VEGF therapy followed by renal biopsy between 2006 and 2013. They found that 27 patients had variable glomerulopathies, mainly minimal change disease and/or collapsing-like focal segmental glomerulosclerosis (MCN/cFSGS), since 73 patients experienced renal TMA (31).

A systematic review and meta-analysis that involved seven clinical trials with 1850 patients between 1966 and 2006, showed a significant increase in hypertension and proteinuria in individuals taking intravenous bevacizumab in a dose-dependent manner (32).

Bevacizumab therapy was associated with proteinuria development in more than 64% of patients with renal cell carcinoma and 23–38% of patients with colorectal cancer (25). A critical review of VEGF-A signaling and VEGF

receptor in the kidney is required to fully recognize the mechanisms associated with nephrotoxicity while taking VEGF inhibitors. Identifying such mechanisms to reduce VEGF inhibitors-induced nephrotoxicity is essential to increase cancer patients' survival by taking VEGF inhibitors (33).

Some renal critical downstream signaling pathways of VEGF inhibition include MAPK (mitogen-activated protein kinase)/ERK (extracellular signal-regulated kinase), endothelial nitric oxide synthase, and mammalian target of rapamycin (mTOR). VEGF-A inhibition directly through VEGF trap or antibody binding is related to the development of TMA. Tyrosine kinase inhibition, MAPK/ERK pathway inhibition, and mTOR inhibition lead to glomerulopathies (e.g., minimal change nephropathy and/or FSGS), tubulointerstitial injury, and albuminuria, respectively (33).

Several cases of deteriorating hypertension, deteriorating proteinuria, renal function perturbation, TMA, and glomerular disease are reported following intravitreal VEGF inhibition. Hanna et al confirmed that switching from a more potent drug to a lower potency one is necessary in some cases. For example, in some patients with diabetic proliferative retinopathy and diabetic macular edema who showed worsening of proteinuria and hypertension after receiving intravitreal bevacizumab or aflibercept, switching to ranibizumab was beneficial (34). Moreover, the less absorbed anti-VEGF agents with a shorter half-life and lower potency may cause an overall improvement in both hypertension and proteinuria (34). There are several mechanisms by which anti-VEGF agents may cause hypertension and proteinuria (Figure 1).

Anti-VEGF in patients with chronic kidney disease and dialysis

Increased hypertension and proteinuria in patients with CKD or diabetic nephropathy after anti-VEGF administration is explicable. However, no clinical study has displayed a higher risk of proteinuria or hypertension for cancer patients with simultaneous CKD or on dialysis. Pharmacokinetic analysis indicated that estimated glomerular filtration rate (eGFR) does not affect the apparent clearance of VEGF-targeted drugs. It is suggested that reduced renal function and ESRD should not be considered as a contraindication for VEGF-targeted drugs. A retrospective study involving 520 patients with renal cell carcinoma who received bevacizumab, sunitinib, or sorafenib concluded that VEGF-targeted therapy's efficacy was not influenced by renal function at the beginning of therapy (35). Generally, the pharmacokinetic properties and toxicities reported in patients with CKD undergoing dialysis and received sunitinib were similar to patients without CKD, except for a higher prevalence of treatment-induced hypertension (36,37). Although regular follow-up of renal function and proteinuria in patients with CKD and ESRD is necessary, dose modification is not suggested. However, anti-cancer therapy withdrawal is recommended only at the beginning of nephrotic syndrome or persistent hypertension (38). Furthermore, larger prospective trials to determine the renal safety of intravitreal anti-VEGF treatment, especially in at-risk groups such as those with CKD, are necessary. These trials may use renal markers, including eGFR (estimated glomerular filtration rate), albumin to creatinine ratio and cystatin C, in addition to evaluating the prevalence of AKI and CKD.

Conclusion

Anti-angiogenic therapy is an original and efficient pathway for the treatment of angiogenesis-dependent diseases. Due to their ability to prevent angiogenesis, VEGF inhibitors have advanced as powerful tools to treat angiogenesis-dependent diseases, such as cancer and diabetic retinopathy. VEGF preserves the kidney structure and function in normal physiologic conditions. Therefore, all treatments inhibiting the VEGF pathway may lead to
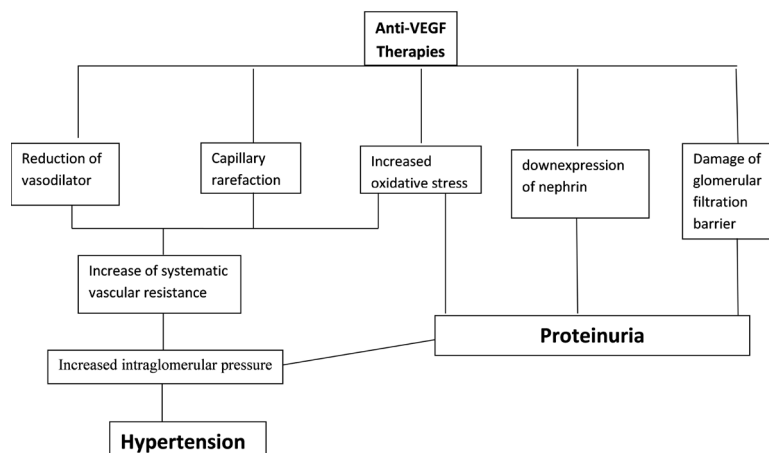

Figure 1. Mechanisms that anti-VEGF drugs may cause hypertension and proteinuria.

renal disorders, mainly renovascular diseases involving proteinuria, hypertension, nephrotic syndrome, decreased GFR, and TMA. Some related reports and associated mechanisms, especially for hypertension and proteinuria, were reviewed in the present study.

Authors' contribution

SSB, RS and MM were the principal investigators of the study. AM participated in preparation of the concept and design. SA revisited the manuscript and critically evaluated the intellectual contents. LS left valuable comments on English errors. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

None.

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