Research Opportunities in Interventional Nephrology

By Prabir Roy-Chaudhury

Interventional nephrology is in the midst of an exponential growth phase, with data from the U.S. Renal Data System suggesting that at least 25 percent of total vascular access procedure costs are billed by nephrologists (1). Indeed, it is likely that the growth of interventional nephrology as a distinct discipline within nephrology has played an important role in the success of process-of-care initiatives, such as Fistula First, which has raised the arteriovenous fistula (AVF) prevalence rate from 34 percent in December 2003 at the start of this initiative to 59.5 percent as of August 2011 (2). Despite these positive indicators, however, dialysis vascular access dysfunction remains a huge clinical problem. Specifically, almost 80 percent of incident hemodialysis patients start with a tunneled dialysis catheter (TDC) (3), only 40 percent of AVFs are suitable for hemodialysis between 4 and 5 months after surgery (4), and the 1-year primary patency for polytetrafluoroethylene (PTFE) dialysis access grafts is only 23 percent (5). Clearly, we need to do better!

Although there are multiple biological and process-of-care reasons for these problems (6–10), we believe that an important underlying cause of these clinical problems is a relative lack of focused basic science, translational, clinical, and process-of-care (outcome) research in the field of dialysis vascular access.

In addition, the induction of formal, high-quality research initiatives into interventional nephrology programs in particular could potentially transform the standing of this distinct discipline within nephrology within both nephrology and internal medicine. Thus, research programs in this area could go a long way toward enhancing the standing of interventional nephrology in the eyes of nephrology program and division directors, and they could constitute an important step toward making interventional nephrology a true distinct discipline within nephrology akin to transplant nephrology. Such research programs could also help bring interventional nephrology into academic institutions. This is absolutely essential for the future of interventional nephrology. Sustained long-term growth of this distinct discipline will likely occur only if it has a solid base within academia while at the same time maintaining its close links with the community physician base that has allowed this specialty to grow so rapidly.

The first publication that attempted to identify core areas of research in vascular access was the 2006 Kidney Disease Outcomes Quality Initiative on vascular access (11), which identified several areas for possible research investigation, including patient preparation, selection and placement of hemodialysis access, cannulation of fistulae and grafts, detection of access dysfunction, treatment of fistula and graft complications, and prevention of catheter complications.

More recently, a survey sent out to the membership of the American Society of Diagnostic and Interventional Nephrology identified (a) arteriovenous fistula maturation, (b) process-of-care guidelines for the creation and maintenance of dialysis vascular access, and (c) PTFE graft stenosis as the three most pressing areas for research into dialysis vascular access, in the order described.

In addition, the ASN's Interventional Nephrology Advisory Group of the American Society of Nephrology (INAG) in combination with the council of the American Society of Diagnostic and Interventional Nephrology recently submitted several areas for research investigation to the Kidney Research National Dialogue sponsored through the National Institute of Diabetes, Digestive and Kidney Diseases. In addition to the areas described previously, improvement in long-term dialysis outcomes, optimization of endovascular and surgical

procedures, and the use of TDC coatings were highlighted as key areas for research activities in this field.

Clearly, there are many potential areas for research in this field and also at least some consensus on a priority ranking for investigative efforts. What is needed, however, is a mechanism to enable the research to be done successfully.

Although there are many approaches to investigative research in dialysis vascular access, the key issue in many ways is the establishment of a system or a process that encourages long-term research activity in this field. One approach, which has been espoused by INAG as a way to lay a firm foundation for a long-term commitment to research activity in this field, is to support the establishment of several academic dialysis access centers (ADACs). These centers will (a) establish basic or translational research programs focused on dialysis vascular access, (b) develop clinical research programs (both investigator initiated and industry sponsored), and (c) establish dedicated (1-year) interventional nephrology training programs where nephrology fellows will be trained not just to do procedures but also in the biology, epidemiology, and process of care of dialysis vascular access.

We believe that the establishment of such ADACs will not only increase the opportunities for well-funded high-quality research in this area but also play a key role in allowing interventional nephrology to grow, by establishing a place for this distinct discipline within nephrology within academic institutions. Finally, although these ADACs are likely to have a home within divisions of nephrology, it is critical that they retain a multidisciplinary nature, because dialysis vascular access dysfunction is by definition a multidisciplinary problem, which we believe can be solved only through a multidisciplinary and translational research effort.

In summary, we believe that this is the time to aggressively develop a formal structure for focused research into dialysis vascular access. We know the problems, and we are asking the questions that need to be asked. In addition, we are lucky that the past decade has seen phenomenal advances in bioengineering, drug delivery, nanotechnology, and cellular therapies, all of which could have a positive impact on dialysis vascular access. We need to apply these biological and technological advances (combined with outcomes and process-of-care research) to the clinical problem of dialysis vascular access so that we can improve on the care we provide our patients. The development of high-quality research programs focused on dialysis vascular access is essential for this to be achieved.

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vomiting. The data described below reflect the safety profile of VOTRIENT in 290 RCC patients who participated in a randomized, double-blind, placebo-controlled study *[see Clinical Studies (14) of full prescribing information]*. The median duration of treatment was 7.4 months (range 0 to 23) for patients who received VOTRIENT and 3.8 months (range 0 to 22) for the placebo arm. Forty-two percent (42%) of patients on VOTRIENT required a dose interruption. Thirty-six percent (36%) of patients on VOTRIENT were dose reduced. Table 1 presents the most common adverse reactions occurring in ≥10% of patients who received VOTRIENT.

Table 1. Adverse Reactions Occurring in ≥10% of Patients who Received VOTRIENT

	VOTRIENT (N = 290)			Placebo (N = 145)		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
Adverse Reactions	%	%	%	%	%	%
Diarrhea	52	3	<1	9	<1	0
Hypertension	40	4	0	10	<1	0
Hair color changes	38	<1	0	3	0	0
Nausea	26	<1	0	9	0	0
Anorexia	22	2	0	10	<1	0
Vomiting	21	2	<1	8	2	0
Fatigue	19	2	0	8	1	1
Asthenia	14	3	0	8	0	0
Abdominal pain	11	2	0	1	0	0
Headache	10	0	0	5	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Other adverse reactions observed more commonly in patients treated with VOTRIENT than placebo and that occurred in <10% (any grade) were alopecia (8% versus <1%), chest pain (5% versus 1%), dysgeusia (altered taste) (8% versus <1%), dyspepsia (5% versus <1%), facial edema (1% versus 0%), palmar-plantar erythrodysesthesia (hand-foot syndrome) (6% versus <1%), proteinuria (9% versus 0%), rash (8% versus 3%), skin depigmentation (3% versus 0%), and weight decreased (9% versus 3%). Table 2 presents the most common laboratory abnormalities occurring in >10% of patients who received VOTRIENT and more commonly (≥5%) in patients who received VOTRIENT versus placebo.

Table 2. Selected Laboratory Abnormalities Occurring in >10% of Patients who Received VOTRIENT and More Commonly (≥5%) in Patients who Received VOTRIENT Versus Placebo

	VOTRIENT (N = 290)			Placebo (N = 145)		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
Parameters	%	%	%	%	%	%
Hematologic						
Leukopenia	37	0	0	6	0	0
Neutropenia	34	1	<1	6	0	0
Thrombocytopenia	32	<1	<1	5	0	<1
Lymphocytopenia	31	4	<1	24	1	0
Chemistry						
ALT increased	53	10	2	22	1	0
AST increased	53	7	<1	19	<1	0
Glucose increased	41	<1	0	33	1	0
Total bilirubin increased	36	3	<1	10	1	<1
Phosphorus decreased	34	4	0	11	0	0
Sodium decreased	31	4	1	24	4	0
Magnesium decreased	26	<1	1	14	0	0
Glucose decreased	17	0	<1	3	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Hepatic Toxicity: In a controlled clinical study with VOTRIENT for the treatment of RCC, ALT >3 X ULN was reported in 18% and 3% of the VOTRIENT and placebo groups, respectively. ALT >10 X ULN was reported in 4% of patients who received VOTRIENT and in <1% of patients who received placebo. Concurrent elevation in ALT >3 X ULN and bilirubin >2 X ULN in the absence of significant alkaline phosphatase >3 X ULN occurred in 5/290 (2%) of patients on VOTRIENT and 2/145 (1%) on placebo. *[See Dosage and Administration (2.2) of full prescribing information and Warnings and Precautions (5.1).]* **Hypertension:** In a controlled clinical study with VOTRIENT for the treatment of RCC, 115/290 patients (40%) receiving VOTRIENT compared with 15/145 patients (10%) on placebo experienced hypertension. Grade 3 hypertension was reported in 13/290 patients (4%) receiving VOTRIENT compared with 1/145 patients (<1%) on placebo. The majority of cases of hypertension were manageable with anti-hypertensive agents or dose reductions with 2/290 patients (<1%) permanently discontinuing treatment with VOTRIENT because of hypertension. VOTRIENT has been associated with hypertensive crisis in patients with various cancer types including RCC. In the overall safety population for RCC (N = 586), one patient had hypertensive crisis on VOTRIENT. *[See Warnings and Precautions (5.6).]* **QT Prolongation and Torsades de Pointes:** In a controlled clinical study with VOTRIENT, QT prolongation (≥500 msec) was identified on routine electrocardiogram monitoring in 3/290 (1%) of patients treated with VOTRIENT compared with no patients on placebo. Torsades de pointes was reported in 2/586 (<1%) patients treated with VOTRIENT in the RCC studies. *[See Warnings and Precautions (5.2).]* **Arterial Thrombotic Events:** In a controlled clinical study with VOTRIENT, the incidences of arterial thrombotic events such as myocardial infarction/ischemia [5/290 (2%)], cerebral vascular accident [1/290 (<1%)], and transient ischemic attack [4/290 (1%)] were higher in patients treated with VOTRIENT compared to the placebo arm (0/145 for each event). *[See Warnings and Precautions (5.4).]* **Hemorrhagic Events:** In a controlled clinical study with VOTRIENT, 37/290 patients (13%) treated with VOTRIENT and 7/145 patients (5%) on placebo experienced at least 1 hemorrhagic event. The most common hemorrhagic events in the patients treated with VOTRIENT were hematuria (4%), epistaxis (2%), hemoptysis (2%), and rectal hemorrhage (1%). Nine (9/37) patients treated with VOTRIENT who had hemorrhagic events experienced serious events including pulmonary, gastrointestinal, and genitourinary hemorrhage. Four (4/290) (1%) patients treated with VOTRIENT died from hemorrhage compared with no (0/145) (0%) patients on placebo. *[See Warnings and Precautions (5.3).]* In the overall safety population in RCC (N = 586), cerebral/intracranial hemorrhage was observed in 2/586 (<1%) patients treated with VOTRIENT. **Hypothyroidism:** In a controlled clinical study with VOTRIENT, more patients had a shift from thyroid stimulating hormone (TSH) within the normal range at baseline to above the normal range at any post-baseline visit in VOTRIENT compared with the placebo arm (27% compared with 5%, respectively). Hypothyroidism was reported as an adverse reaction in 19 patients (7%) treated with VOTRIENT and no patients (0%) in the placebo arm. *[See Warnings and Precautions (5.8).]* **Diarrhea:** Diarrhea occurred frequently and was predominantly mild to moderate in severity. Patients should be advised how to manage mild diarrhea and to notify their healthcare provider if moderate to severe diarrhea occurs so appropriate management can be implemented to minimize its impact. **Proteinuria:** In the controlled clinical study with VOTRIENT, proteinuria has been reported as an adverse reaction in 27 patients (9%) treated with VOTRIENT. In 2 patients, proteinuria led to discontinuation of treatment with VOTRIENT. *[See Warnings and Precautions (5.9).]* **Lipase Elevations:** In a single-arm clinical study, increases in lipase values were observed for 48/181 patients (27%). Elevations in lipase as an adverse reaction were reported for 10 patients (4%) and were Grade 3 for 6 patients and Grade 4 for 1 patient. In clinical RCC studies of VOTRIENT, clinical pancreatitis was observed in 4/586 patients (<1%). **Cardiac Dysfunction:** Pazopanib has been associated with cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure) in patients with various cancer types, including RCC. In the overall safety population for RCC (N = 586), cardiac dysfunction was observed in 4/586 patients (<1%).

7 DRUG INTERACTIONS

7.1 Drugs That Inhibit or Induce Cytochrome P450 3A4 Enzymes

In vitro studies suggested that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Therefore, inhibitors and inducers of CYP3A4 may alter the metabolism of pazopanib. **CYP3A4 Inhibitors:** Coadministration of pazopanib with strong inhibitors of CYP3A4 (e.g., ketoconazole, ritonavir, clarithromycin) may increase pazopanib concentrations. A dose reduction for VOTRIENT should be considered when it must be coadministered with strong CYP3A4 inhibitors *[see Dosage and Administration (2.2)]*. Grapefruit juice should be avoided as it inhibits CYP3A4 activity and may also increase plasma concentrations of pazopanib. **CYP3A4 Inducers:** CYP3A4 inducers such as rifampin may decrease plasma pazopanib concentrations. VOTRIENT should not be used if chronic use of strong CYP3A4 inducers can not be avoided *[see Dosage and Administration (2.2)]*.