Isosorbide Mononitrate For Anti-Vascular Endothelial Growth Factor (VEGF) Induced Kidney Injury

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SPECIFIC AIM:

To test the hypothesis that isosorbide mononitrate prevents deterioration of renal function in patients receiving anti-angiogenic therapies that target vascular endothelial growth factor (VEGF).

BACKGROUND AND SIGNIFICANCE: Anti-angiogenic drugs that target VEGF (bevacizumab) and its receptors (sunitinib, sorafenib, pazobanib, and axitinib) are part of standard treatment for patients with renal cell carcinoma, non-small cell lung carcinoma, colorectal carcinoma, and gastrointestinal stromal tumors[1]. However, because of their action on VEGF expression levels, the use of these medications has been associated with significant kidney damage and hypertension. Indeed, the use of anti-angiogenic therapies is frequently halted in cancer patients because of worsening kidney function, hypertension, and proteinuria with the subsequent delay, interruption or reduction of effective dose in patients requiring this treatment modality[1].

Importantly, many of the kidney-related side effects of antiangiogenic and anti-VEGF therapies have been attributed to the downregulation of nitric oxide (NO) bioavailability[1]. In support of a modulatory effect of VEGF on NO, it has been shown that VEGF infusion results in a significant drop in blood pressure mainly through stimulation of eNOS (endothelial NO synthase) and consequent NO release[2,3]. NO activation and enhanced synthesis lead to vasodilation in the renal microvasculature, which results in lowering of blood pressure and other modulatory effects on kidney function.

PRELIMINARY STUDIES: Cancer patients receiving anti-VEGF therapy share similar pathophysiological renal changes as seen in women with preeclampsia[8,9]. Endothelial dysfunction in pre-eclampsia results from reduction in NO bioavailability [4]. Interestingly, eNOS uses nitrates as a substrate, and hence several studies have examined the utility of using organic nitrates as a possible treatment for NO deficiencies in preeclampsia. Although these studies were not powered to identify alterations in maternal and fetal outcomes, they did highlight the potential use of organic nitrates as antihypertensive agents in pre-eclampsia [5,6,7]. Moreover, recent studies have shown that NO donors normalize blood pressure in anti-VEGF induced hypertension[10]. The same authors went on to devise a treatment algorithm distinguishing three groups of patients on anti-VEGF treatment: normotensive (<120/<80 mm Hg); prehypertensive (120-130/80-89 mm Hg) and hypertensive (>140/>90 mm Hg). They suggested no pharmacological treatment for normotensive patients, starting NO donors only for those pre-hypertensives with evidence of organ damage, and starting with NO donors as antihypertensive agents for the hypertensives along with weekly blood pressure checks[11]. In their paper, they suggest that pre-treatment with long lasting NO donors may protect against the development of VEGF pathway inhibitor (VPI)- induced hypertension. They suggest the start of treatment 7-10 days before the initiation of VPI therapy. The paucity of large clinical studies in the literature using NO donors to protect against the development of proteinuria and hypertension and cancer patients receiving VPI therapy prompted us to investigate this modality of treatment.

RATIONALE OF DOSE: Preliminary data from a trial done to study single dose effects of isosorbide mononitrate (IMN) alone or in combination with losartan on central blood pressure showed that the mean placebo-subtracted decrease from baseline in augmentation index was highest in those patients who received 60 mg IMN with or without losartan [12]. An effectiveness of extended release nitrate study for treatment of systolic hypertension used 60 mg and 120 mg strength tablets and showed statistically significant changes in the augmentation index and decreasing pulse pressure [13]. No studies have checked the effect on proteinuria. Accordingly, 60 mg and 120 mg of IMN will be used in the present study

SAFETY OF ISOSORBIDE MONONITRATE: The FDA indication for IMN is for prevention of angina pectoris (https://druginserts.com/lib/rx/meds/imdur/). Per the package insert as referenced in link, there is no evidence of carcinogenicity, gene mutation or chromosome aberrations at biologically relevant concentrations. Side effects include nausea, dizziness, headache, symptomatic hypotension

MATERIAL AND METHODS:

Study Population: Adult patients who are referred to the Adult Nephrology Clinic at The University of Texas Health Science Center at Houston for evaluation and treatment of acute kidney injury, hypertension and/or proteinuria while either on or enrolled with anti-VEGF therapies, will be included in the study. The protocol is currently being submitted to the University of Texas Health Science Center at Houston IRB. Informed consent in the native language of each patient will be obtained prior to enrollment.

Inclusion Criteria: Patients on or enrolled for anti-VEGF therapy and having new-onset proteinuria, defined as a urine protein: creatinine ratio (UPC) of >500mg/g or hypertension (Systolic BP ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg) or a decrease in eGFR by ≥ 25% from baseline before starting therapy.

Exclusion Criteria: Pregnant women and breast-feeding women. Patients >65 years will be excluded.

Protocol and Treatment Plan: The patients will have baseline blood pressure (BP), UPC, weight, serum basic metabolic panel and eGFR measured prior to being assigned into groups. All current prescribed and over the counter medications will be documented. Patients will be allocated to the treatment or placebo arms by simple randomization. BP will be measured in the right arm of patients, in the seated position, using arm cuff and automated office blood pressure by oscillometry method. Three measurements will be taken one minute apart, and the average of each of the systolic and diastolic measurements will be charted as the blood pressure recording for the visit. Pregnancy and breast feeding status will be established by self-reporting by female patients.

Patients in the treatment arm will be started on IMN 60 mg ER daily. The dose of IMN will be escalated to 120 mg ER (two tablets of 60 mg ER) after 4 weeks of start of therapy, if no response as per our response criteria (as below) is achieved. The grace period for follow up appointments would be +/- 3days to account for clinic closure, weather changes or patient's inability to come to clinic due to non-medical reasons.

The drug and placebo will be compounded in Compounding Shop Pharmacy, 11845 Wilcrest Dr, Houston, TX 77031. Even though we will be using the drug for a non-FDA approved use of IMN, we will not be needing IND for the study drug due to the low risk profile of the drug. Drug accountability by IDS will include for storage, labeling, dispensing and disposal of the study drug and placebo.

Criteria for Response (one or more of the following)

1. Improved eGFR ≥25% from prior to enrollment.
2. Reduction in proteinuria of ≥25% from prior to enrollment.
3. Reduction in SBP of ≥ 10 mm Hg and/or DBP ≥ 5 mm Hg from prior to enrollment

Study design:

The patients will be allocated by simple randomized into the two groups (20 patients per group). The study will bedouble-blinded

Group 1: *(Treatment group)*. The starting dose will be Imdur 60 mg ER daily and after 4 weeks, if tolerated but response is not achieved, the dose will be escalated to Imdur 120 mg ER daily (2 tabs of 60 mg ER tablets). This would be done in addition to the standard of care treatment with either angiotensin converting enzyme inhibitor (ACEI) or calcium channel blockers to treat hypertension as needed.

Group 2 :(*Placebo group)*: Placebo will be given along with the standard of care treatment with either ACE I or calcium channel blockers to treat hypertension as needed. The tablets of placebo will be doubled after 4 weeks of start of therapy. This will help eliminate bias in this double-blinded study.

Follow-up: Systolic BP will be monitored on a weekly basis for three months. The patients will record their BPs at home with their automated machines and will either call in with the results or bring their records during the next clinic visit. The eGFR and serum creatinine (included in the basic metabolic panel) will be measured as per protocol laboratory workup done within 15 days of enrollment. This will be done once a month during clinic visits. The grace period for follow up appointments would be +/- 3 days to account for clinic closure, weather changes or patient's inability to come to clinic due to non-medical reasons. A follow up phone call will be done every month (weeks 6, 10, 14 and 17 weeks) for 3 months. Antihypertensive medications that the patients have been taking prior to enrollment will be continued. Any reduction in the need for antihypertensive medications will be documented. UPC will be measured at the time of enrollment and then monthly.

Primary End Points:

- Reduction in UPC of ≥25% from that measured before enrollment

Secondary End Points:

- Improved eGFR ≥25% from before enrollment.
- Reduction in SBP of ≥ 10 mm Hg and/or DBP ≥ 5 mm Hg from before enrollment

Both the primary and secondary outcomes will be measured for every month for the 3 months that the patient is in the trial. All patients will continue treatment for the entire 3 months to help with data analysis for future larger randomized controlled studies. The grace period for follow up appointments would be +/- 3days to account for clinic closure, weather changes or patient's inability to come to clinic due to non-medical reasons.

MONITORING/ EVALUATION DURING STUDY:

Baseline BP, serum creatinine, eGFR, and UPC will be recorded at the time of enrollment. For blood testing 2cc of serum will be collected and for urine testing 2 ml of urine will be collected, and sent to the Memorial Herman outpatient laboratory. Blood pressure will be monitored on a weekly basis starting from the time of enrollment. In those who are already on BP medications, BPs will be recorded on a weekly basis, and any need for reduction/increase in the doses/addition of new medications will be document. Patients will be given a log book to record their BPs. Patients will be monitored for 3 months. UPC and serum creatinine will be measured on a monthly basis.

If side effects (nausea, dizziness, headache, symptomatic hypotension) are observed to the increased dose of 120 mg/day, the dose will be reduced back to the 60 mg d.

Confidentiality Plan:

All data obtained, including concomitant medications will be entered in Red Cap. All serious adverse events will be forwarded to FDA according to the UT Health Science Center at Houston institutional policy. All records will be maintained at UT Heath Science center. The Data Safety Monitoring board will be involved in safety monitoring.

Possible Side Effects:

Minor side effects of Imdur have been noted, including headache, dizziness, hypotension and nausea. As per FDA approved package insert, headache and dizziness was reported in >5% of the patients. These symptoms are dose dependent and tend to disappear with continued use.

Criteria for Removal:

With the increased dose of Imdur, if side effects such as symptomatic hypotension, nausea, headache or dizziness the dose will be reduced to 60 mg ER. If it is the starting dose (60 mg ER) which caused these effects, then the patient will be taken off the drug, and will be observed for Intension to Treat (ITT) analysis. The Severe Adverse Effect (SAE) will be reported according to the UT Health Science Center at Houston institutional policy. Criteria for removal would be uncontrolled nausea, headache, symptomatic hypotension or dizziness. We will also monitor for any worsening of renal function or proteinuria.

Limitations:

This is a pilot study and therefore it is may not be powered to detect difference with treatment. The small sample size may not allow the data to be statistically significant. It is unclear if other antihypertensive medications will confound the results. Once preliminary data is available, the study population will be increased for a larger clinical trial.

Expected results:

There will be statistically significant response seen with therapy in the patients. The study is a pilot study and will help in establishing the basis of a larger randomized controlled study.

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