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Potential of Minocycline for Treatment of Resistant Hypertension

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Blood pressure (BP) control is suboptimal in many treated hypertensive individuals; up to a quarter have treatment-resistant hypertension (RHTN, uncontrolled BP despite lifestyle modification and 3 antihypertensive drugs at/near maximal tolerated doses).[1] RHTN conveys a high risk for adverse events. Exploring novel concepts and mechanisms could accelerate identification of new management targets. Our studies, primarily with rodent models of human hypertension, inform our hypothesis of a ***dysfunctional brain-gut communication***.[2] Our overarching postulate indicates that prohypertensive signals (stress, inactivity, etc.) increase sympathetic and dampen parasympathetic drives, sequentially leading to gut dysbiosis, leakiness, and pathology. These actions alter plasma metabolic and immune profiles important in neuroinflammation, increase BP, and perpetuate high BP leading to RHTN. Thus, neuroinflammation and dysbiosis are critical in RHTN.[3] Minocycline, an anti-inflammatory antibiotic, crosses the blood-brain barrier and reduces BP in animal HTN models.[4,5] Accordingly we tested our hypothesis in a pilot study of RHTN patients.

The IRB-approved study was conducted in ambulatory RHTN patients with documented cardiovascular disease (CVD) and/or type-2 diabetes, and all subjects provided voluntary written informed consent. Briefly, high-risk adults with RHTN receiving stable-dose antihypertensive medications for >3 months were enrolled. Age >85 years, orthostatic hypotension, or contraindications to tetracyclines were exclusions. A dose-finding (100 mg *vs* 200 mg bid) open-label study was planned to determine the lowest minocycline dose to reduce mean daytime ambulatory systolic BP (dAMBP) ≥5 mmHg ("Responder") (Study 1, ClinicalTrials.gov NCT02133872), followed by a placebo-controlled, double-blind, crossover trial at that dose and assessment of activated microglia in brain autonomic regions by PET[6] (Study 2, ClinicalTrials.gov NCT02133885). However, an early patient initially receiving 200 mg bid reported lightheadedness/dizziness with a BP 88/50 mmHg, which drove protocol modification for the safety of these high-risk patients to an open-label dose-finding effort beginning at 50 mg bid, escalating to 100 and 200 mg bid in nonresponsive subjects.

We recruited 40 patients; 14 either failed screening or withdrew (primarily after dissatisfaction with ambulatory BP monitoring [ABPM]), and baseline characteristics of the remaining 26 are summarized (Figure A). All patients were taking ≥3 antihypertensive medications and, because they were high risk, it was not possible (nor ethical) to withdraw antihypertensive drugs. At visit 1, participants had unattended automated office BP (Office) measured three times (Omron HEM-907XL), were instructed in measuring home BP thrice weekly, and were fitted for 24-hour ABPM (Spacelabs 90207). At visit 2, minocycline was initiated with follow-up every 2-4 weeks. Visits 4, 8, and 12 included ABPM. Participation ended upon achievement of a decline in mean systolic dAMBP of ≥5 mmHg ("Responders"). Visits 5 and 9 were by phone, reminding patients to return for titration or continue minocycline and return for a final visit. Dose titrations occurred at visits 6 (100 mg bid) and 10 (200 mg bid) if target dAMBP was not achieved. Pill counts assessed minocycline adherence; patients were queried about antihypertensive medications and adverse effects.

Mean systolic dAMBP decreased significantly (primary outcome), among all 26 patients and also for the 16 (62%) responders (Figure B, Systolic, *red*). Actual BP levels at baseline (Figure C, left) and post-minocycline (Figure C, right) appear for all patients (top) and minocycline responders (bottom) where 10, 2 and 4 patients responded at doses of 50, 100, 200 mg bid, respectively. Mean reductions in dAMBP (132/73 to 127/70) and office BP (131/71 to 125/68) occurred (all patients) and 134/72 to 122/66 (responders). Interestingly, at nighttime, only systolic AMBP was significantly reduced during minocycline. No change occurred in body weight during minocycline. Limited modeling of mean dASBP indicated baseline mean systolic dAMBP and plasma cholesterol negatively predicted this BP response to minocycline. One patient reported lightheadedness with BP 88/50 mmHg, which resolved with antihypertensive drug down-titration; 4 others with asymptomatic hypotension also required antihypertensive drug down-titration. No other treatment-related adverse effects were reported.

Since Th17 cells are implicated in trans-endothelial/epithelial migration among disorders involving gut inflammation[7], we enumerated circulating $CD4^+$ inflammatory cells containing $CD161^+$ $IL17^+$ and $CCR6^+$ $ITGb7^+CD161^+$ $IL17^+$ markers (flow cytometry, 9 patients). These subfractions declined significantly during minocycline [-20% (-40 to-0.1) and -3.4% (-6.5 to -0.3), respectively] in responders. Minocycline was associated with reduced BP and decreased active microglia[5] in a responder (Figure D).

This is the first reported human trial investigating whether minocycline mitigates impaired brain-gut communication associated with RHTN via anti-inflammatory properties. These results extend our findings from animal models.[4,5] Minocycline has anti-inflammatory properties, penetrates the blood-brain barrier, and inhibits microglia activation and neuroinflammation. Our evidence from experimental animals documents minocycline's antihypertensive effects are likely mediated by anti-

A Selected Baseline Characteristics	All Patients N=26 (100%)	Responders n=16 (100%)
Age: years, mean	64	61
Men	12 (46)	6 (37)
Race: white	13 (50)	7 (44)
Body mass index: kg/m^2, mean	37	37
Smoker	14 (54)	6 (38)
Diabetes	18 (69)	10 (62)
Coronary artery disease	6 (23)	5 (31)
Peripheral artery disease	3 (12)	2 (12)
Cerebrovascular disease	2 (8)	1 (6)
Chronic kidney disease	3 (12)	1 (6)
Number of antihypertensive drugs =3	18 (70)	8 (50)
Number of antihypertensive drugs ≥4	8 (31)	8 (50)
Type of antihypertensive drug		
RAS blockers: ACEIs/ARBs	26 (100)	16 (100)
Aldosterone antagonists	5 (19)	4 (25)
Beta blockers	19 (73)	12 (75)
Calcium channel blockers	16 (62)	10 (62)
Diuretics: thiazide/thiazide-like	20 (77)	12 (75)
Diuretics: loop	5 (19)	4 (25)
Diuretics: potassium sparing	5 (19)	4 (25)
Alpha blockers	2 (8)	2 (12)
Arteriolar vasodilators	2 (8)	1 (6)

C	Baseline		During Minocycline		p=SBP/DBP
All (n=26)	SBP	DBP	SBP	DBP	
Office	141 136-146	79 75-83	137 132-141	81 77-85	0.0176 >0.05
24hAMBP	131 126-137	71 67-74	125 121-130	68 65-70	0.0007 0.008
dAMBP	132 127-137	73 69-76	127 122-132	70 67-71	0.0097 0.0109
nAMBP	128 121-135	66 61-69	121 115-128	62 58-66	0.008 >0.05
Minocycline Responders (n=16)					
Office	144 136-151	82 77-87	136 130-142	82 77-88	0.0028 >0.05
24hAMBP	134 127-141	72 67-77	122 117-128	66 64-70	0.0001 0.0007
dAMBP	135 129-142	74 70-79	124 118-129	68 65-71	0.0001 0.0007
nAMBP	128 119-138	64 58-70	118 111-126	60 56-64	0.001 >0.05

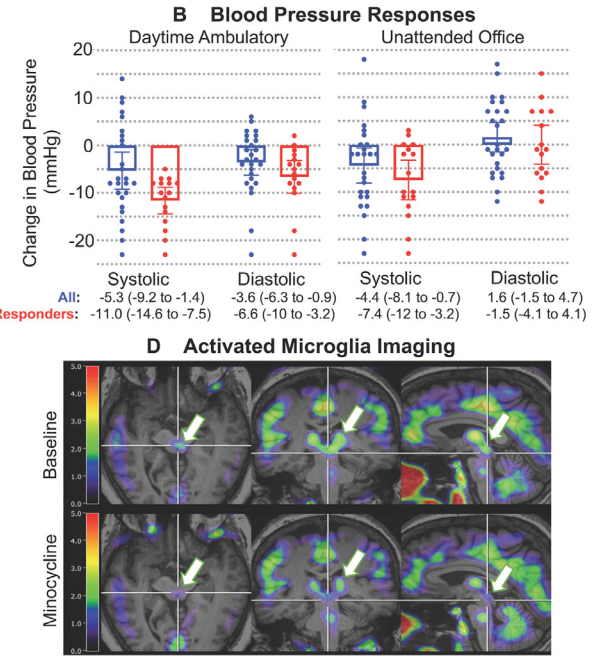

Figure. In Inpatients with resistant hypertension, minocycline was associated with reduced blood pressure and decreased markers of gut-brain axis dysfunction. A. Selected Baseline Characteristics. There were similar numbers of men and women and black and white Americans (by chance there were no Hispanic subjects). Overall, the patients all had cardiovascular disease and/or type 2 diabetes with documented hypertension for at least 5 years. Additionally, they were predominantly obese, smokers, with hyperlipidemia taking ≥3 antihypertensive drugs of different pharmacological classes at or near maximally tolerated doses. ACEI = angiotensin-converting enzyme inhibitor. ARB = angiotensin receptor blocker. RAS = renin-angiotensin system. B. Blood Pressure Responses. Minocycline significantly reduced average daytime ambulatory systolic blood pressure in all 26 patients. In 16 of these 26, the mean reduction was 5 mmHg ("Responders," primary outcome, Systolic, left), mean daytime diastolic blood pressure (Diastolic, right), and unattended office systolic blood pressure (Systolic, and diastolic blood pressure, right). For each patient, changes in blood pressure data (baseline - minocycline) are shown in the vertical plots. Values below the vertical plots are means and 95% confidence intervals. Prism 8 was used for statistical analyses. C. Actual Blood Values. BP data for all 26 patients (upper panel) and the 16 minocycline responders (lower panel) from baseline (left) to during minocycline (right). Data are mmHg, mean and 95% CIs and p-values from paired t-test. Prism 8 was used for statistical analyses. D. PET brain images of a minocycline responsive patient overlaid on T1-weighted MR images showing reduction of ^{11}C-PBR28 binding in both thalamic and periaqueductal gray regions. Top images-baseline, and bottom images-minocycline. The scale shows non-displaceable binding potential (BPnd) of ^{11}C-PBR28, a Translocator Protein (TSPO) receptor-ligand as a marker for activated microglia. BPnd was calculated using the Logan graphic method with the cerebellar gray matter as a reference region.[5] White arrows point to regions with microglia activation changes during minocycline treatment.

inflammatory action inhibiting brain microglia activation. Data here support this contention in RHTN as the dose (50 mg bid) was not likely high enough to be an effective antibiotic, thus, it would be expected to show little effect on microbiome diversity. However, a dysfunctional brain-gut axis mediated by impaired autonomic regulation of gut function and its microbiome cannot be excluded. This is particularly relevant since autonomic dysregulation is associated with gut dysbiosis in neurological diseases and now also in RHTN.

This first-in-human pilot trial provides important information to support a mechanism-based, larger, randomized, placebo-controlled clinical trial to establish minocycline or a modified tetracycline derivative as a therapeutic option for RHTN.

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Competing Interest

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Left Ventricular Hypertrophy-Low Longitudinal Strain Phenotype in Elderly Patients with Preserved or Mid-range Ejection Fraction

The left ventricular hypertrophy-low longitudinal strain phenotype in elderly patients with preserved or mid-range ejection fraction has been proposed to identify patients at a high risk of clinical events.[1] In addition, this phenotype may carry a high prevalence of cardiac amyloidosis, specifically transthyretin cardiac amyloidosis.[2] A structured screening tool in the echocardiographic laboratory can flag these patients and alert the treating team. We aimed at examining the performance of echocardiographic screening of elderly patients with left ventricular hypertrophy-low longitudinal strain phenotype and preserved or mid-range ejection fraction, and studied the short-term outcomes for these patients.

The echocardiographic screening protocol was implemented in the Echocardiography laboratory at Mount Sinai Morningside and used the following criteria: (1) patient age ≥70 years; (2) left ventricular posterior wall thickness ≥1.3 cm; (3) left ventricular ejection fraction ≥45%; and (4) global longitudinal strain >-16%. If the patient met all the screening criteria, the team was notified of the findings and further evaluation for possible cardiac amyloidosis was suggested. The subsequent evaluation and management of the patient was carried out by the primary team as clinically indicated.

This was a retrospective cohort study of a 100 consecutive alerts issued from January 2020 to August 2021. The patients were followed up to 12 months since the index echocardiogram by retrospective chart review for the occurrence of major cardiovascular events (MACE) as the composite primary outcome. The components of MACE included all-cause mortality, myocardial infarction, stroke, and cardiac hospitalization. The study protocol was approved by Mount Sinai Institutional Review Board.

Echocardiographic analysis was performed using established criteria as outlined in the American Society of Echocardiography guidelines.[3] The comparisons were performed using the Student's *t* test or Wilcoxon rank-sum test for continuous variables, and the chi-square test for categorical variables. Univariate and multivariate regression analysis was used to explore the associations of clinical and echocardiographic variables with MACE.

Among 100 patients, the mean age was 80.5 (standard deviation, SD 6.7) years, 56% were women, and 24% were outpatients. Shortness of breath was the study indication in 28% of patents, and 20% had established heart failure (ACC/AHA stage C). The patients carried a high burden of co-morbidities including hypertension (91%), diabetes mellitus (45%), previous myocardial infarction (10%), previous percutaneous coronary intervention (20%), previous coronary bypass grafting surgery (7%), and chronic kidney disease (34%). The median BNP level was 560 ng/L (interquartile range, IQR 264 to 1217), and the median creatinine level was 1.3 mg/dl (IQR 0.95 to 2.3). On echocardiographic analysis, mean left ventricular mass index was 134 g/m^2 (SD 34), left atrial volume index was 40.5 ml/m^2 (SD 15.6), global longitudinal strain was -11.6% (SD 2.6), and left ventricular ejection fraction was 59.8% (SD 11.1).

Among 100 study patients, 34 patients underwent amyloidosis evaluation which included 33 Tc 99m pyrophosphate scans using both planar and SPECT imaging, 5 cardiac magnetic resonance imaging, and 4 tissue biopsies. In 66 patients subsequent evaluation was not pursued by the clinical team. Overall, 16 patients (16% of the overall cohort) were diagnosed with cardiac amyloidosis: 15 TTR type and 1 AL type (Figure 1).

There were 37 MACE, including 14 deaths among 100 patients with the average follow-up of 9 months (Figure 1). No significant age or gender differences were seen among patients who did and did not experience MACE but patients who experienced MACE had a higher body mass index (27.9 vs 25.2 kg/m^2, $p = 0.02$). The patients did not show statistical differences in co-morbidity distributions, with the exception of stage C heart failure (35% vs 11%, $p < 0.01$) and atrial fibrillation/flutter (41% vs 21%, $p = 0.03$) being more prevalent in patients who experienced MACE. Among echocardiographic variables, patients who experienced MACE had higher estimated RA pressure (6.2 vs 4.5 mm Hg, $p = 0.02$) and lower right ventricular s' velocity (9.9 vs 11.8 cm/sec, $p < 0.01$). Similarly, these patients had worse left ventricular global longitudinal strain (-10.8 vs -12.2%, $p = 0.03$). At the same time, no significant differences were observed in left ventricular volumes and ejection fraction, left atrial volume index, right ventricular size, TAPSE, medial and lateral early diastolic tissue velocities, mitral E velocity, and stroke volume index. In multivariate logistic regression analysis using backward elimination strategy, the following variables were independently