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ORIGINAL RESEARCH

Minocycline in Severe Cerebral Amyloid Angiopathy: A Single-Center Cohort Study

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BACKGROUND: Evidence from animal studies suggests that minocycline may reduce lobar intracerebral hemorrhage (ICH) recurrence in cerebral amyloid angiopathy, possibly by inhibiting perivascular extracellular matrix degradation in cerebral small vessels. There is currently no evidence of its safety or efficacy in humans with cerebral amyloid angiopathy.

METHODS AND RESULTS: To provide preliminary data to support future studies of minocycline's efficacy, the authors performed a retrospective single-center cohort study to assess the incidence of recurrent ICH in patients with an aggressive clinical course of probable cerebral amyloid angiopathy who had been prescribed minocycline off-label via shared decision-making. Crude incidence rate ratios were calculated to compare incidence rates before versus after treatment. Sixteen patients (mean age at minocycline initiation, 66.3±3.5 years; women 62.5%; median of 3 lobar ICHs [range, 1–6]) were initiated on minocycline and followed for a median of 12.4 months (range, 1.8–61.4 months). Adverse events were reported in 4 of 16 patients (gastroenteric, n=3; dizziness, n=1) and were considered mild. ICH incidence sharply increased the year before minocycline initiation compared with the preceding years (2.18 [95% CI, 1.50–3.07] versus 0.40 [95% CI, 0.25–0.60] events per patient-year) and fell to 0.46 (95% CI, 0.23–0.83) events per patient-year afterwards. Incidence rate ratios of recurrent ICH after minocycline was lower (0.21 [95% CI, 0.11–0.42], $P<0.0001$) compared with the year before initiation.

CONCLUSIONS: Minocycline appeared safe and generally tolerated in a small group of patients with clinically aggressive cerebral amyloid angiopathy and was associated with reduced ICH recurrence. Determining whether this reduction represents a biological response to minocycline rather than a regression to the mean, however, will require a future controlled treatment trial.

Key Words: cerebral amyloid angiopathy ■ intracerebral hemorrhage ■ matrix metalloproteinases ■ minocycline ■ preliminary study

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Current guidelines offer approaches to reducing risk for recurrent intracerebral hemorrhage (ICH) related to cerebral amyloid angiopathy (CAA) such as consideration of discontinuing antithrombotic agents and controlling blood pressure,[1] but no disease-modifying therapies for CAA have been identified. Evidence from human brain tissue has pointed to a vessel-remodeling step promoting rupture of CAA-affected vessels,[2] with animal studies suggesting that extracellular matrix degradation in particular is a potential contributor to this process.[3] Amyloid-beta deposition appears to activate metalloproteinase (MMP)-2 and MMP-9 in the perivascular extracellular matrix, potentially leading to basal membrane degradation and spontaneous ICH.[4,5] Minocycline, a US Food and Drug Administration (FDA)–approved second-generation tetracycline for the indication of acne vulgaris, has demonstrated pleiotropic pharmacologic effects including inhibiting MMP-2/-9 activity.[6] It has also shown efficacy in reducing the risk of spontaneous ICH in CAA animal models,[7] but data on human patients are lacking. We report the results from a small cohort of patients with CAA treated with off-label minocycline via shared decision-making.

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CLINICAL PERSPECTIVE

What Is New?

- This study provides preliminary tolerability and outcome data on minocycline use in patients with severe cerebral amyloid angiopathy.
- Minocycline was overall safe and tolerated in this patient population, and we found hints of a possible reduction in intracerebral hemorrhage recurrence.

What Are the Clinical Implications?

- This preliminary cohort study provides useful insights for the design of a controlled clinical trial comparing cerebral amyloid angiopathy patients treated with minocycline versus cerebral amyloid angiopathy patients treated with best medical care to support minocycline efficacy for reducing intracerebral hemorrhage recurrence risk in severe cerebral amyloid angiopathy.

Nonstandard Abbreviations and Acronyms

CAA	cerebral amyloid angiopathy
FDA	Food and Drug Administration
ICH	intracerebral hemorrhage
IR	incidence rate
IRR	incidence rate ratio
MMP-2	metalloproteinase 2
MMP-9	metalloproteinase 9

METHODS

Anonymized data supporting the findings of this study are available from the corresponding author upon reasonable request. This study was approved by the Massachusetts General Hospital (MGH) institutional review board and reported following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist. We performed a single-center retrospective cohort study of patients diagnosed with probable CAA according to the Boston criteria 2.0[8] who were referred to the MGH outpatient stroke service and prescribed minocycline. Minocycline was prescribed off-label by the treating stroke neurologist because of a patient's aggressive disease course, typically multiple symptomatic ICHs over a relatively short time interval. Initiation of minocycline was performed with the consent of patient and family members using a shared decision-making model[9] in which patient and family members were informed that the use of this medication was supported by laboratory but not human data, that it was not FDA-approved for this indication, and that there were no FDA-approved medications for prevention of CAA-related ICH. The starting dosage was typically a 100-mg tablet taken twice per day, the highest FDA-recommended minocycline dosage for long-term use in adults,[6] and was adjusted downward by the treating physician as needed based on patient tolerance.

Patients' Identification

Patients included in the study were identified both by active and passive search: in the former case, we searched the Research Patient Data Registry, a centralized warehouse for electronic medical records at MGH, with the query Minocycline-CAA to retrieve all possible patients with CAA treated with minocycline in our center from January 1, 2003 to February 1, 2023. The latter method consisted in directly contacting all MGH Stroke Service neurologists known to see outpatients with CAA. We included only patients who received at least 2 weeks of minocycline treatment, as we hypothesized that any effect on CAA would not occur immediately after initiation. Clinical variables were retrieved through electronic medical records, and incident ICH assessment was made through all available follow-up neuroimaging. The first reported CAA-related ICH was considered as the retrospective start date for pre-minocycline ICH monitoring. The follow-up time was censored to the most recent clinical evaluation available as of August 15, 2023. Data S1 provides further details on data collection and neuroimaging assessment.

Minocycline Treatment

We collected data regarding minocycline starting and maintenance dose, side effects, interruptions, and restarts. The start date was ascertained from the electronic medical records when available, otherwise it was estimated based on the available information. Patient-years treated with minocycline were calculated dividing the total sum of minocycline treatment years by the total treated population. Eventual periods of drug suspension were accounted for by including any follow-up available within 4 weeks after interruption, either temporary or definitive. This time interval was chosen as a reasonable period in which the minocycline effect on vascular remodeling could still be potentially active after drug interruption.

Outcome Definition

The outcome was defined as new symptomatic ICH after minocycline initiation. Because of the indication bias for initiating minocycline treatment following periods of particularly high ICH incidence, ICH diagnosed before drug initiation was categorized a priori into 2 temporal intervals: (1) ≤1 year before minocycline

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initiation, and (2) >1 year before minocycline. An additional time point at 4 months after initiation of treatment was chosen post hoc to explore the effect of minocycline after a potentially sufficient time interval to demonstrate the clinical impact on vascular remodeling.

Statistical Analysis

Continuous variables were summarized with mean and SD if normally distributed and median and range if otherwise. Categorical variables were summarized with percentages. Crude ICH incidence rates (IRs) with 95% CIs were calculated across the prespecified time intervals followed by calculation of crude IR ratios (IRRs) to compare IRs across the different time frames. The null hypothesis of no effect (IRR=1) was tested with the significance level set at 0.05. Statistical analysis was performed using R Studio version 2023.06. Data S1 describes smoothed hazard rates estimation for the first ICH recurrence and sensitivity analyses testing a shorter follow-up time after treatment interruption and the effect of death attrition.

RESULTS

Of 33 patients screened for eligibility (Figure 1), 16 who received at least 2 weeks of off-label minocycline treatment for CAA were identified and analyzed (Table 1). The mean age at minocycline initiation was 66.3±3.5 years, and 62.5% were women; all were diagnosed with sporadic CAA except 1 patient diagnosed with hereditary CAA due to the Piedmont mutation.[10] Treated individuals had a median of 3 lobar hemorrhages (range, 1–6) at the time of minocycline initiation. Neuroimaging biomarker characterization is available in Data S1.

ICH Risk Factors

Hypertension was prevalent (13 of 16 patients) but BP was generally within control targets in the time frames prespecified <1 year before and <6 months after minocycline initiation (56.2% versus 58.3%, respectively). Among other potential ICH risk factors, no patients averaged daily or greater alcohol use, 56.2% used statin medications pre-minocycline initiation (falling to 21.4% post-minocycline), 50% used selective serotonin reuptake inhibitor/serotonin noradrenaline reuptake inhibitor pre-minocycline, one patient used low-dose aspirin (for the indication of concomitant intravascular device), and none used other antithrombotic agents.

Minocycline: Dosage, Adverse Events, and Treatment Interruptions

The minocycline starting dose was 200 mg/d in 11 of 16 patients, 100 mg/d in 4 of 16 patients, and 150 mg/d

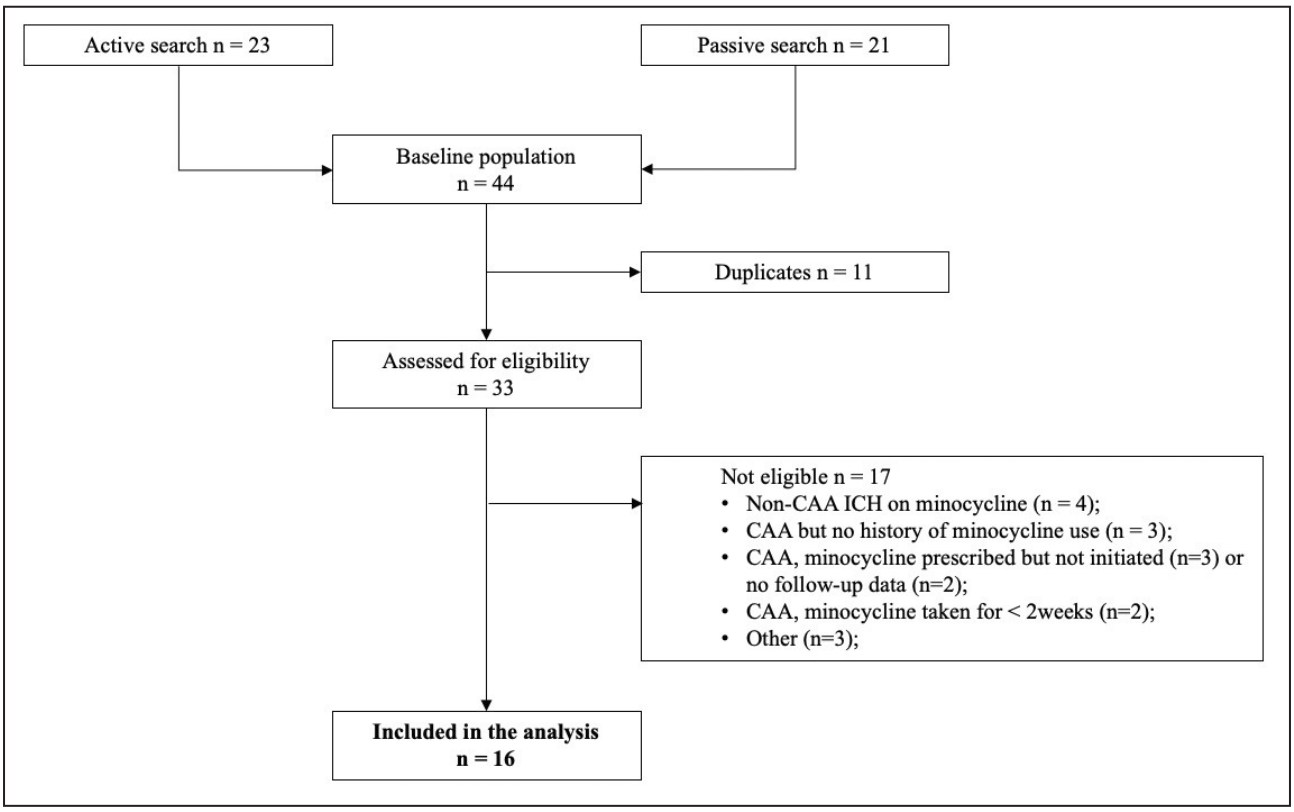

Figure 1. Study population flowchart.
CAA indicates cerebral amyloid angiopathy; and ICH, intracerebral hemorrhage.

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Table 1. Demographics and Vascular and Intracerebral Hemorrhage Risk Factors of the Study Population (n=16)

Variable	Mean (SD), median (range), or n (%)
Age, y	
At first visit	64.1 (4.5)
At minocycline initiation	66.3 (3.5)
Female sex	10 (62.5%)
White race	15 (93.7%)
Follow-up, median (range), y	5.9 (0.3–12.4)
Before minocycline	3.8 (0.1–10.4)
After minocycline	1.0 (0.1–5.1)
Diabetes	3 (18.7%)
Hypertension	13 (81.2%)
Mean blood pressure <130/80 mm Hg	
1 y Before minocycline	9 (56.2%)
6 mo After minocycline	7 (58.3%)*
Dyslipidemia	11 (68.7%)
Alcohol use	12 (75%)
≥1 Drink per wk	7 (43.7%)
≥1 Drink per d	0 (0%)
Smoke ever	10 (62.5%)
Five years before minocycline	1 (7.1%)†
Statin ever	9 (56.2%)
After initiation of minocycline	3 (21.4%)‡
SNRI/SSRI during 5 y preinitiation of minocycline‡	8 (50%)
After initiation of minocycline	4 (50%)§
Atrial fibrillation	1 (6.2%)

SNRI/SSRI indicates serotonin noradrenaline reuptake inhibitor/selective serotonin reuptake inhibitor.

Only 2 patients had apolipoprotein E genotype available (*E3E3* and *E2E4*, respectively).

*Missing data (n=4).

†Missing data (n=2).

‡Missing data (n=2).

§Missing data (n=8).

in 1 of 16 patients. Adverse events were reported in 4 of 16 patients and consisted of gastroenteric symptoms (gastric pain, n=2; diarrhea, n=1) and dizziness (n=1). Overall median follow-up time taking minocycline was 12.4 months (range, 1.8–61.4 months), and 6 of 16 patients interrupted treatment, 3 of whom did so because of adverse events: 1 with diarrhea who temporarily interrupted treatment and resumed at the same dosage (200 mg), 1 with gastric pain who resumed at a lower dose (200 mg initially, resumed at 100 mg) but interrupted again thereafter for symptoms recrudescence, and 1 with dizziness who interrupted permanently. Two other individuals discontinued minocycline permanently after hospitalization for ICH recurrence. Finally, 1 individual self-discontinued after an intermitting severe acute respiratory syndrome coronavirus 2 infection and resumed after 9.7 months. The median follow-up time of minocycline use was 12.4 months (range, 1.8–61.4 months) for the individuals who did not interrupt treatment and 9.3 months (range, 2.2–31.2 months) for those who interrupted treatment.

Recurrent ICHs

The crude IRs for ICH (Table 2) sharply increased the year before minocycline initiation when compared with the preceding years (2.18 versus 0.40 events per patient-year), then fell to 0.46 events per patient-year after minocycline initiation. When analyzing the post-minocycline period, the first 4 months maintained a higher IR (1.06 events per patient-year), which dropped substantially (to 0.32) thereafter. These rate fluctuations are displayed as IRRs in Figure 2, with reduced risk of recurrent ICH after minocycline when compared with the year preceding minocycline initiation (IRR, 0.21 [95% CI, 0.11–0.42]; $P<0.0001$). Smoothed hazard rates for first ICH and sensitivity analysis for the effect of death attrition are shown in Figures S1 and S2, respectively.

DISCUSSION

This retrospective cohort study describes the use of oral minocycline, prescribed off-label under a shared decision-making model, in 16 patients with an aggressive course of recurrent CAA-related ICH. The patients' clinical characteristics show adequate treatment of modifiable ICH risk factors, in particular generally acceptable blood pressure control and low rates of heavy alcohol consumption (Table 1). Minocycline was generally well tolerated, though with gastrointestinal upset effects that are characteristic of this medication.

We found reduced rates of ICH recurrence over a median of 12.4 months post-minocycline initiation follow-up compared with the 1-year preinitiation period. The apparent reduction in ICH recurrence may well reflect regression to the mean following initiation of therapy for the indication of frequent ICH recurrence. This interpretation is consistent with the similarity of post-tinitiation ICH recurrence to that observed during the

Table 2. Crude IRs for ICH Overall and At Any Time Point Before and After Minocycline Initiation

Time interval	No. of events	Person-y at risk	IR (95% CI)
Total	66	93.5	0.71 (0.55–0.90)
Before minocycline	55	70.0	0.78 (0.59–1.02)
>1 y	22	54.9	0.40 (0.25–0.60)
≤1 y	33	15.1	2.18 (1.50–3.07)
After minocycline	11	23.5	0.46 (0.23–0.83)
≤4 mo	5	4.7	1.06 (0.34–2.47)
>4 mo	6	18.7	0.32 (0.12–0.69)

ICH indicates intracerebral hemorrhage; and IR, incidence rate.

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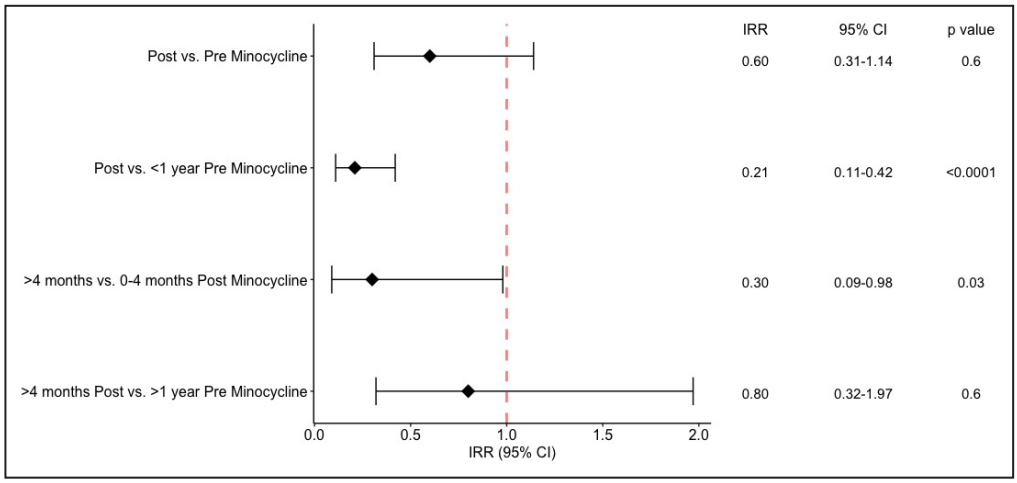

Figure 2. Forest plot for unadjusted incidence rate ratios (IRRs) comparing intracerebral hemorrhage incidence rates before and after minocycline at different time points (P<0.05).

time interval >1 year preinitiation. This small data set also raises the possibility of actual medication-related reduction in ICH recurrence, however, as recurrence rates appeared to remain relatively high during the first 4 months postinitiation (potentially before the onset of minocycline's impact on prohemorrhagic vascular changes) and to decline after 4 months of treatment.

In their study, Yan et al[7] observed reduced hemorrhagic lesions associated with minocycline treatment in 2 transgenic mouse models that developed advanced CAA with hemorrhage: Tg2576 mice (which overexpress the amyloid precursor protein containing the Swedish mutation) and 5×DAF/apoE4 mice (created by crossing mice containing 5 familial Alzheimer disease mutations with mice containing knock-in of the apolipoprotein E4 gene). Analysis of brain from the mice showed no effect of minocycline on CAA burden but reduced expression of multiple inflammatory markers including MMP-2 and MMP-9, as well as higher amounts of tight junctions and basal lamina proteins. These results are consistent with evidence pointing to metalloproteinase activation and perivascular inflammation as potential contributors to the process of vascular remodeling postulated to cause amyloid-laden cerebral vessels to rupture and bleed[2–5] and highlight plausible targets for minocycline's pleiotropic pharmacologic effects.[6]

This study has prominent limitations, most notably the small sample size (adequate only to provide univariate and unadjusted estimates of ICH IRs), a high potential for confounding by indication, and the absence of a comparator arm of untreated individuals with aggressive CAA. We also note that one of the treated patients had a genetic form of CAA, which might confer a more severe clinical trajectory than sporadic disease. The data were intended to provide preliminary information on the tolerability and safety of this candidate treatment in individuals with the most aggressive courses of probable CAA. Any inferences about the relative benefits and risks of minocycline as a CAA therapy will require considerably larger and better controlled studies. In this light, our data might provide useful insights for the design of clinical trials testing minocycline efficacy in CAA, in particular: (1) the average treatment effect size of minocycline on ICH risk reduction, although unadjusted; (2) the expected prevalence and severity of side effects; and (3) the expected treatment adherence and dropout rates.

Our data suggest that minocycline is safe and reasonably well tolerated in a small group of patients with CAA and hints at possible benefits in risk of recurrent ICH in patients with aggressive disease. These findings help support the planning of future larger-scale trials.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Data S1
Figures S1–S2

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