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Feasibility of minocycline and doxycycline use as potential vasculostatic therapy for brain vascular malformations: pilot study of adverse events and tolerance

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Abstract

Background: Tetracyclines may be useful in preventing pathological vascular remodeling, thus decreasing the risk of spontaneous hemorrhage from brain vascular malformations. ***Methods*:** Arteriovenous malformation (AVM) and intracranial aneurysm patients undergoing non-invasive management were treated with minocycline or doxycycline (200mg/day) up to 2 years in a prospective open-label safety pilot trial. The primary outcome was to compare dose limiting intolerance (DLI), defined as treatment-related dose-reduction and withdrawal between the agents. ***Results:*** 26 patients with AVMs (n=12) or aneurysms (n=14) were recruited. Adverse event rates were similar to other reported trials of these agents; four of 13 (31%) minocyline and three of 13 (23%) doxycycline patients had DLI (hazard ratio=3.1, 95%CI=0.52-18.11, log rank p =0.70,). ***Conclusions:*** It is feasible to propose a long-term trial to assess the potential benefit of tetracycline therapy to decrease hemorrhagic risk in brain vascular malformations.

Introduction

Tetracycline-class drugs are emerging as clinically applicable non-specific MMP inhibitors that have the potential to enhance vascular stability, thus reducing the risk of spontaneous hemorrhage. They also possess neuroprotective properties. Settings investigated to date include cerebral ischemia [1], intracranial hemorrhage (ICH) [2,3], neurodegenerative disorders [4,5], traumatic brain injury [6], and atherosclerotic disease[7]. In clinical trials, tetracyclines decreased MMP in abdominal aortic aneurysms (AAA) and carotid plaques [7-9]. We have preliminary data that doxycycline can reduce MMP levels in brain arteriovenous malformation (BAVM) tissue [10]. Further, both AVMs [11] and intracranial aneurysms [12] display inflammation as part of their lesional phenotype. Tetracyclines appear to generally display anti-inflammatory properties, beyond their anti-MMP effects [13].

Unlike cancer-related chemotherapy that aims to shrink abnormal tumor tissue as *cytotoxic* therapy [14], MMP inhibition is not necessarily intended to obliterate the brain vascular malformation. Rather, the concept would be to stabilize vascular tissue and thereby decrease the risk of spontaneous ICH, i.e., a *vasculostatic* approach.

Although tetracyclines have been studied extensively, long-term studies are rare. Further, none of the studies have targeted patients with intracranial vascular diseases. We performed this Phase I study to document the expected tolerance and adverse events in the same population, on whom Phase II trials would be conducted. This study was designed to test the feasibility of using minocycline and doxycycline as potential long-term vasculostatic therapy for brain vascular malformations, and estimate frequency and nature of adverse events that might be expected from a larger Phase II or Phase III trial effort. We hypothesized that there would be no difference in tolerability to minocycline and doxycycline treatment in patients with cerebrovascular diseases.

Methods

This was a prospective open-label safety pilot trial, using minocycline or doxycycline treatment for patients with BAVM and IA for up to 2 years. The primary outcome was to estimate dose limiting intolerance (DLI) in this patient cohort and compare DLI between the two agents; DLI was defined as treatment related dose-reduction or study withdrawal. The secondary outcome was to examine laboratory values indicative of potential tetracycline-related hemological, hepatical and renal toxicity. The Institutional Committee on Human Research approved the study protocol, and all patients gave written consent before enrollment. The study was registered with ClinicalTrials.gov (NCT00243893).

Study population

Patients with *untreated* BAVMs or aneurysms were recruited at the University of California, San Francisco. Patients had elected not to undergo invasive therapy, usually as a result of being deemed untreatable by conventional means. Other inclusion criteria were patients aged 13 and older; BMI within 30% of normal; white blood cell (WBC) > 3,800/mm^3, creatinine ≤ 2.0 mg/dl and alanin aminotransferase (ALT) ≤ 2 times upper limit of normal. Exclusion criteria included patients with unstable medical illness, e.g., unstable angina or advanced cancer over the last 30 days; contraindications to tetracyclines, including allergy or other intolerance; prior tetracycline use within 2 months of baseline visit; history of systemic lupus erythmatosis or vestibular disease, except benign positional vertigo; history of non-compliance with treatment or other experimental protocols.

Study medication

Patients received either oral doxycycline or minocycline (100mg twice a day). This dose was based on prior clinical trials that demonstrated a significant reduction of plasma MMP-9 [9]

and tissue MMP-9 in AAA patients [7,9]. Our previous pilot experiments with AVM tissue showed similar effects [10]. Besides the study drug and the experimental procedures, there was no change in patient management.

Follow-up assessment

Follow-up was conducted through telephone contact (weekly in the first 3 months, monthly for the next 3 months, and quarterly thereafter), laboratory evaluations, and patient reports of suspected adverse events. Adverse events and intercurrent neurological events were monitored. Compliance was monitored by patient self-report, phone contacts and monthly assessment of pill counts by returned blister packages. Levels of creatinine and ALT, hemoglobin, platelets and WBC were measured at baseline, then 3 months, 6 months, and every 6 months thereafter.

Management of side effects

The general algorithm for treating side effects was a stepwise progression, based in part on the initial severity of the side effect: (a) counsel patient on preventative measures; if unsuccessful, then (b) temporarily interrupt medication for one week or reduce to once a day dosing. If (b) was successful, the patient resumed normal dosage. If not, (c) discussion took place with primary physician to either try dose reduction again or, as a last resort, consider withdrawal from trial.

Serious adverse events (SAEs) were defined according to the FDA MedWatch definition (death, life-threatening, hospitalization, disability, or required intervention to prevent permanent impairment or damage).

Statistical Methods

If a patient could not resume the protocol-specified dose after the temporary interruption or dose reduction, then this was counted as the endpoint, DLI. Comparison of the study drugs was analyzed using Kaplan-Meier survival curves with a log-rank test, and a Cox regression to adjust for patient's age, gender and disease type.

Differences in baseline group characteristics were evaluated using Mann-Whitney-U test, and categorical variables were analyzed using two-sided Fisher's exact test. Differences in lab values between groups over time were tested using repeated measures with a general linear model. All reported values were mean ± SD, unless stated otherwise. A two-sided p value less than 0.05 was considered statistically significant.

Results

Overview and baseline characteristics of patient population

Twenty-six *untreated* patients with BAVMs (n=12) or aneurysms (n=14) were enrolled in the study (**Table 1)**. To date, 10 patients have completed 2 years of treatment. The mean follow-up duration was 17.6±7.7months for doxycycline and 18.7±7.2 months for minocycline. No significant differences were found between the study groups regarding baseline clinical characteristics. Nine patients are still actively receiving drug with remaining study time ranging from 1 to 15 months.

Adverse events, patient retention and compliance with study medications

Treatment-related adverse events occurred in 13 of the 26 patients enrolled, resulting in 3 (11.5%) dose reductions and 5 (19.2%) withdrawals. Two of 3 patients with dose-reduction tolerated the 100 mg daily dose subsequently and finished the 2-year course, while one later withdrew from the study. In addition, 3 events were judged as not treatment-related, including 2 SAEs (1 ICH leading to death after taking doxycycline for 22 months and 1 ICH after taking minocycline for 18 months), and 1 drop-out due to lack of desire to continue being in the study. Overall tolerability as indicated by DLI was 69% for minocycline and 77% for doxycycline. Kaplan-Meier survival analysis (**Figure 1**) showed no difference of DLI between treatment groups (log rank p=0.70), but DLI showed a trend that was greater in the minocycline group compared to doxycycline (HR [95% CI] = 3.06 [0.52-18.11], P=0.217), after controlling for the effects of female gender [HR=13.4 (1.4-129.4), p=0.03], aneurysms [HR=4.0 (0.6-25.6), p=0.15], and age [HR=0.99 (.95-1.03), p=0.61]. As a sensitivity analysis, we included all events (composite of DLI, 2 hemorrhages and 1 drop-out), and found similar results (log rank p=0.49).

The most reported side effect was photosensitivity (6/26; 23%), followed by vertigo (3/26; 12%), yeast infection (2/26; 8%), gastrointestinal symptoms (2/26; 8%), hyperpigmentation (1/26; 4%), and allergic reaction (1/26; 4%) **(Table 2).** Most of the adverse events were mild and were managed according to the general algorithm. Specifically, photosensitivity and hyperpigmentation were managed by increased skin protection from exposure to ultraviolet light. Vertigo was managed by temporary interruption of the drugs. Yeast infection was treated with antifungal medications. Patients who developed gastrointestinal symptoms were re-counseled to take the drugs with food and not to take them near bedtime. The patient experiencing an allergic reaction withdrew from the study. Yeast infection, vertigo and hyperpigmentation only occurred in the minocycline group, while the allergic reaction only occurred in the doxycycline group. The incidence of side effects was reported more frequently in the minocycline group (61%) than in the doxycyline group (39%), although the difference did not reach statistical significance with our sample size. The 2 incidences of SAEs, 1 hemorrhage each in AVM and aneurysm patients, rendered the annual bleeding rates for them to 5.6% (95% CI = 0.1 – 31.2%) and 5.8% (95% CI = 0.1 – 32.4%), respectively.

Monitoring of laboratory values

Since thrombocytopenia, azotemia and autoimmune hepatitis, although rare, could be potential side effects of tetracyclines, periodical laboratory values of hemological, hepatical and renal function were examined (**Table 3)**. While the WBC decreased over time in the minocycline group compared to the doxycycline ($p<0.01$), creatinine increased in the minocycline group compared to the doxycycline ($p=0.04$). Hemoglobin ($p=0.12$), ALT ($p=0.69$) and platelets ($p=0.45$) showed no difference between the groups. The values for WBC and

creatinine remained within the range of normal values and thus were considered not clinically significant.

Discussion

This study has shown a trend toward more frequent side effects and increased DLI from the minocycline treatment, although the difference between minocycline and doxycycline did not reach statistical significance in this small pilot study. There were no trends showing an increase of adverse events compared to other tetracycline clinical trials [9,15].

The percentage of side effects observed in this study (50%) was similar to, or even slightly lower than, previously reported clinical trials in other cardiovascular or neurological diseases. For instance, 61% of the subjects reported side effects in a multi-center study with six months of doxycycline at the same dosage in AAA patients [9]. The use of broad spectrum antibiotics for extended periods (1-2 yrs) to influence cardiovascular disease, e.g., through treatment of a potential chlamydial infection, has not revealed a significant issue with side effects regarding safety or compliance [16]. In recent trials examining the role of minocycline in neurodegenerative diseases, a futility trial in Parkinson's disease revealed 77% tolerability and reported upper respiratory symptoms, joint pain and nausea as the most common side effects [15].

While the range of adverse events was similar in both drugs, side effects were less frequent in the doxycycline group. In our study population, the rate of gastrointestinal (GI) side effects was very low in both groups, in contrast to others showing that doxycycline was associated with a much higher risk of upper gastrointestinal disorders [17]. Vertigo, consistent with previous reports, occurred only in the minocycline group in our study. In contrast to reported hypersensitivity reactions to minocycline [18], we had only one case in the doxycycline group, and none in the minocycline group. Our monitoring of laboratory values did not reveal

signs of thrombocytopenia, hepatal or renal dysfunction, although they have been documented as side effects by others [19]. None of our patients reported musculoskeletal toxicity, a common side effect in broad-band MMP-inhibitors [20] or lupus-like syndrome, to minocycline [21,22]. Although gender difference related to drug tolerability has not been reported in tetracyclines, our results suggested female gender as a possible predictor for increased intolerance. On the other hand, age did not seem to have an effect on DLI.

The two occurrences of hemorrhage in our study were not unexpected considering prior natural history studies. Increased age, initial hemorrhagic presentation, deep brain location, and exclusive deep venous drainage have been found as independent predictors of AVM hemorrhage in the untreated course after diagnosis [23,24]. Thus, the 82 year old AVM patient with ICH in our study, who was at an advanced age and had a hemorrhagic presentation, could be at elevated risk. The ISUIA study found that aneurysm size and location are predictors of bleeding, with a first year rupture risk of 17% for giant aneurysms, reaching 50% at 5 years for posterior circulation lesions [25]. The aneurysm hemorrhage in our study occurred in a patient harboring a giant basilar tip aneurysm. Our point estimates of the observed hemorrhage rate were 5.6%/yr for AVMs and 5.8%/yr for aneurysms, both of which were well within those reported in previous studies.

We feel that this is an appropriate time to report the overall tolerability and feasibility of the study, since most of the side effect-related withdrawals experienced by the patients occurred within 18 months of the study. To date, the majority of our patients have been enrolled for more than 18 months, making this the longest reported follow-up of tetracycline treatment in neurological and vascular diseases compared to previous trials [7-9,15]. The retention of

patients in this long-term study has been encouraging, as 69% have remained in the two-year treatment course. Other shorter-term tetracycline clinical trials have reported higher retention rates, including 92% in the six-month doxycycline treatment of AAAs [9], and 89% in 12-month minocycline administration with Parkinson's disease. The length of the study appears to be a key factor, given 12 months as the mean time for all withdrawal events in our study. Allowing patients to take the highest tolerated dose, instead of fixed doses, may have reduced withdrawal rates.

This pilot study suggests that long-term tolerability of minocycline and doxycycline in patients with brain vascular malformations is sufficient to support a larger Phase II or III trial to examine efficacy endpoints.

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Table 1. Patient demographics and clinical characteristics.

Treatment	Gender	Age	Disease	Location	Size (mm)	Spetzler Martin Grades
Minocycline	female	19	AVM	occipital,	37	4
	female	53		cortical, subcortical, ventricular, frontal	92	5
	female	15		frontal,	118	5
	male	27		frontal,	45	4
	male	21		thalamic	32	4
	male	21		parasagital, parietal,	34	4
	male	27		cortical, subcortical, frontal, parietal,	61	4
	female	72	aneurysm	basilar	27	n/a*
	male	38		basilar	20	
	male	54		basilar	18	
	male	68		basilar	10	
	male	32		basilar	5	
	male	52		carotid	5	
Doxycycline	female	64	AVM	posterior fossa, cerebellar hemisphere,	40	3
	female	49		temporal, parietal, occipital,	45	3
	female	22		basal ganglia,	35	4
	female	31		parietal,	40	3
	male	34		cortical, subcortical, frontal,	35	4
	female	38	aneurysm	carotid	14	n/a*
	female	15		carotid	4	
	female	56		carotid	20	
	male	40		carotid	12	
	male	70		basilar	18	
	male	49		carotid	5	
	male	61		basilar	10	
	male	78		basilar	7	

*n/a, not applicable

Table 2. Adverse events reported from individual patients.

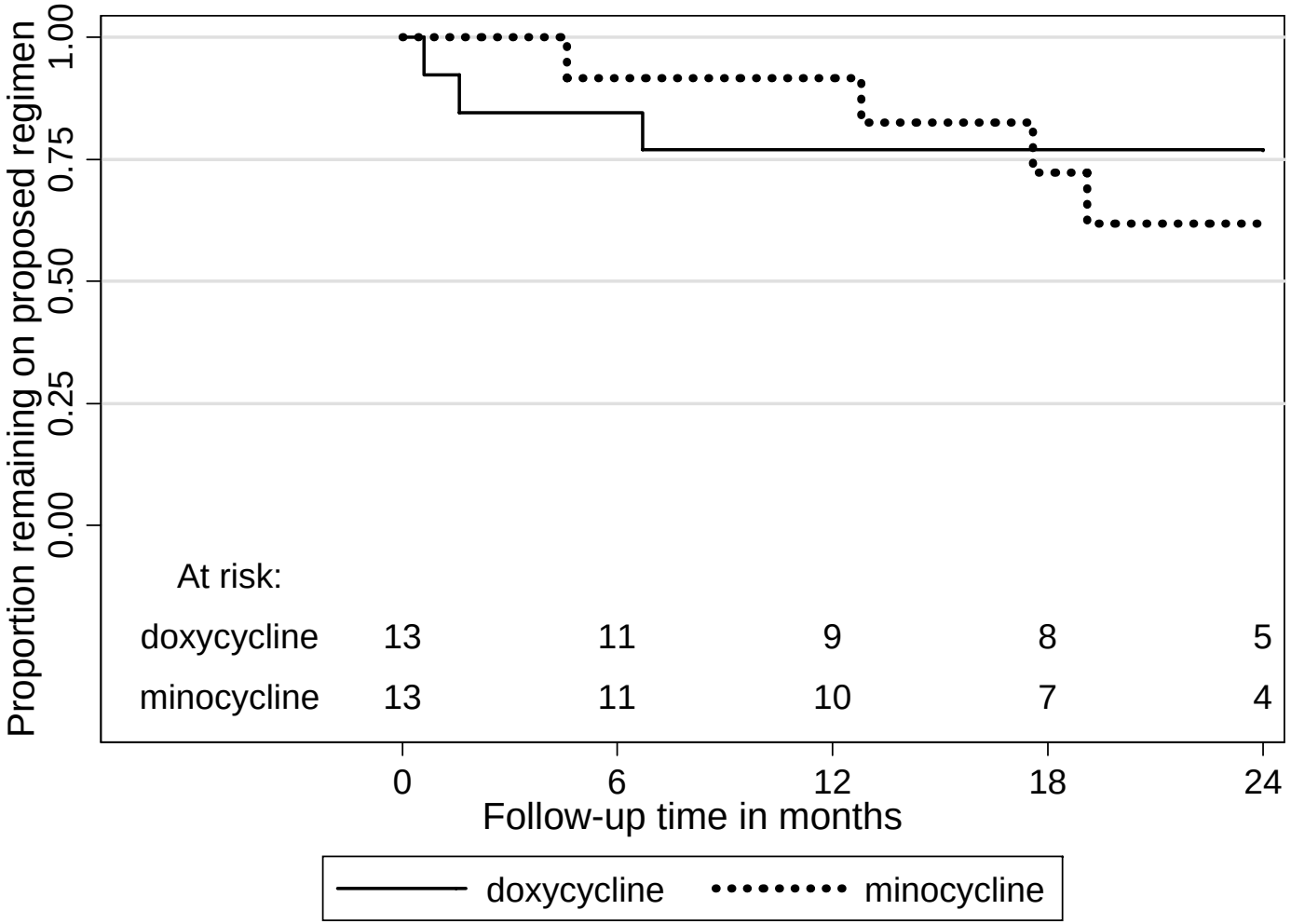
	Patient No.	Yeast	GI	PS	HP	Vertigo	Allergy
Minocycline	1	-	-	-	-	yes	-
	3	-	-	-	-	-	-
	4	-	-	-	-	-	-
	6	-	-	yes	-	-	-
	7	yes	-	-	-	-	-
	8	-	-	-	-	-	-
	10	-	-	yes	yes	-	-
	14	-	yes	-	-	yes	-
	15	yes	-	-	-	-	-
	16	-	-	-	-	-	-
	18	-	-	-	-	-	-
	19	-	-	yes	-	-	-
	26	-	-	-	-	yes	-
Doxycycline	2	-	-	-	-	-	-
	5	-	-	-	-	-	-
	9	-	-	-	-	-	-
	11	-	-	-	-	-	-
	12	-	yes	-	-	-	-
	13	-	-	-	-	-	-
	17	-	-	-	-	-	yes
	20	-	-	yes	-	-	-
	21	-	-	-	-	-	-
	22	-	-	yes	-	-	-
	23	-	-	-	-	-	-
	24	-	-	-	-	-	-
	25	-	-	yes	-	-	-
Minocycline	Total	2 (15%)	1 (8%)	3 (23%)	1 (8%)	3 (23%)	-
Doxycycline	Total	-	1 (8%)	3 (23%)	-	-	1 (8%)
	p	0.48	1.00	1.00	1.00	0.22	1.00

Table 3. Follow-up laboratory tests during the study.

Laboratory Tests	Treatment Groups	Time Points (months)				
		0	3	6	12	18
WBC (1000/µl)	minocycline	5.7±1.3	4.9±0.8	5.4±1.1	5.4±0.9	5.2±1
	doxycycline	6.7±2	6.5±1.2	6.7±2.3	6.4±2	6±0.7
Hemoglobin (g/dl)	minocycline	13.2±1.6	13.7±1.5	13.8±1.4	13.6±1.4	13.6±1.3
	doxycycline	14±1	14.4±0.9	14.3±0.8	14.5±1.1	14.4±1
Platelet (1000/µl)	minocycline	246±39	237±49	244±43	249±52	226±63
	doxycycline	212±63	230±59	235±45	229±62	226±70
Creatinine (mg/dl)	minocycline	1.1±0.3	1±0.2	1±0.2	1±0.2	1±0.2
	doxycycline	0.9±0.2	0.9±0.2	0.8±0.2	0.9±0.3	1±0.2
ALT (unit)	minocycline	19 ±9	19±6	22±10	21±7	22±10
	doxycycline	18±10	20±1	22±14	24±17	15±6

Figure Legend

Figure 1. Kaplan-Meier analysis of time from enrollment to dose reduction or withdrawal (in months).



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