Minocycline Reduces Gadolinium-Enhancing Magnetic Resonance Imaging Lesions in Multiple Sclerosis

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We report a trial of minocycline in people with relapsing-remitting multiple sclerosis (RRMS) that evaluates safety and estimates its effect on magnetic resonance imaging (MRI). Ten subjects with active RRMS received oral minocycline 100mg twice daily for 6 months after a 3-month run-in period. A 30-month treatment extension is ongoing. Clinical and laboratory assessments were completed at enrollment and then at 3-month intervals. MRI was performed at enrolment and then every 4 weeks. Patients without MRI activity during the run-in phase continued in the study, including completion of all MRI scans, to confirm lack of MRI worsening. The primary outcome was change in the mean number of gadolinium-enhancing lesions per scan during the first 6 months of treatment compared with the run-in period (Wilcoxon signed rank test, two-sided alpha of 0.05).

Eighty percent of participants were women. Mean age was 42.8 years (SD 4.0). Mean MS duration was 11.8 years (SD 6.3). Median baseline extended disability status score (EDSS) was 2.5 (range 1.5–5.5). Mean relapse number in the two prior years was 2.6 (range 2–4). During the trial, there were no serious adverse events or laboratory abnormalities and no change in EDSS. Three relapses occurred during the run-in phase, five during the first 6-month treatment phase, and none during the following 6 months. On-treatment relapses included one associated with MRI enhancement (during month 1), two without enhancement (one scan was a post-relapse scan, and one scan was missed because the patient was taking steroids), and two mild truncal sensory attacks unassociated with MRI enhancement (both at 5 months).

Mean total enhancing lesion number decreased from 1.38 lesions per scan during the run-in phase to 0.22 during the treatment phase ($z = 2.204$, $p = 0.0276$), representing a relative reduction of greater than 84%. During the run-in phase, 47.5% of MRI scans (19/40) were active, whereas 9.3% (5/54) were active during the minocycline phase. There were no active scans after month 2 (Fig) and no new active lesions after month 1. Although five patients accounted for all MRI activity before and after treatment, all patient data were included in all analyses.

This study provides preliminary evidence that minocycline may be useful in MS and supports its safety. The MRI results are consistent with the ability of minocycline to inhibit matrix metalloproteinases,[1,2] thus reducing lymphocyte access to the central nervous system. In addition, minocycline may have other beneficial properties including neuroprotection.[3] Small sample size and short trial duration limit conclusions, but reduced MRI activity is encouraging and calls for definitive studies to establish minocycline efficacy in MS.

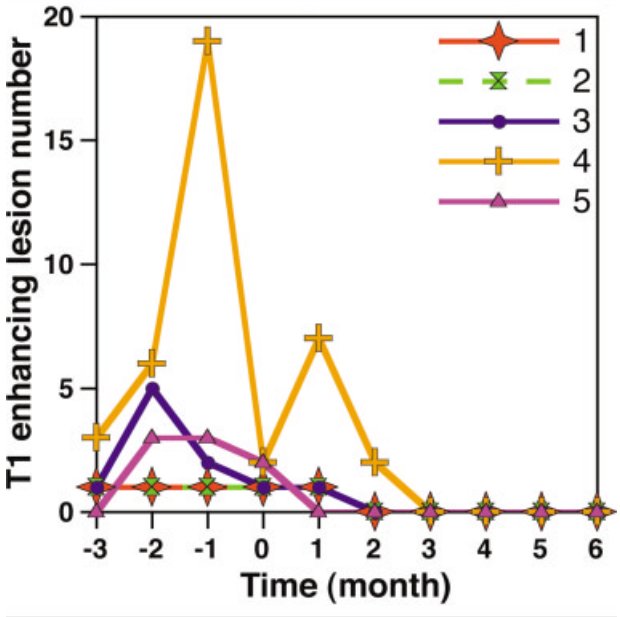

Fig. T1-enhancing lesion number from the magnetic resonance imaging scans of the five patients that exhibited enhancing lesions.

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CCM2 Mutations Account for 13% of Cases in a Large Collection of Kindreds with Hereditary Cavernous Malformations

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Cerebral cavernous malformation (CCM) is a common disorder characterized by abnormally enlarged vascular cavities in the brain without intervening normal parenchyma.[1] It is found in 0.1% to 0.5% of the population and represents 10% to 20% of cerebral vascular lesions.[2] CCM can be inherited dominantly or can occur sporadically and can develop as single or multiple malformations that lead to focal neurological signs, hemorrhagic strokes, seizures, or sometimes death.[3] Recently, mutations in the *MGC4607* gene were found in families that showed linkage to the *CCM2* locus.[4] Consequently, 21 families that are part of the International Familial Cavernous Angioma Study (IFCAS) were screened for mutations in this new *CCM2* gene. Criteria for inclusion in the study were neuroradiological diagnosis by magnetic resonance imaging or histological verification of at least one neuroradiologically diagnosed cavernous malformation of the central nervous system in at least two family members.

The *CCM2* gene codes for the malcavernin protein.[4] It contains 444 amino acids and has a predicted phosphotyrosine-binding (PTB) domain located at amino acids 66 to 224. All 10 exons were screened for mutation by denaturing high-performance liquid chromatography (dHPLC) (Transgenomics, Omaha, NE). Each variant found by the dHPLC then was subsequently sequenced (Applied Biosystems, Foster City, CA). Exon 1 was not screened by dHPLC because of high GC content but was directly sequenced.

We report the identification of three novel mutations segregating in four different families (Fig.). An invariant splice donor site mutation (IVS1+1G→A) was found in exon 1 and an invariant splice acceptor site mutation (IVS3-1G→A) was found in exon 3. In exon 2, a nonsense mutation at amino acid 19 (Arg19Stop) was found to be segregating in two European families, which may indicate a common founder. Degradation of the mRNA may occur through the nonsense mediated decay mechanism unless it is translated leading to a severely shortened protein with no PTB domain.

To date, 45 IFCAS families have been screened for mutations in *CCM1* and *CCM2*. Twenty-two (49%) of these families segregate a *CCM1* mutation,[5] whereas 6 (13%) families contain a *CCM2* mutation (two families previously reported[4]). There remain 17 (38%) families with no *CCM1* or *CCM2* mutations but which will almost certainly have mutations in the nonidentified *CCM3* gene, and possibly in some as yet unidentified CCM locus. More work will be needed, such as the identification of the *CCM3* gene, to further understand the pathological mechanisms involved in the formation of CCMs.

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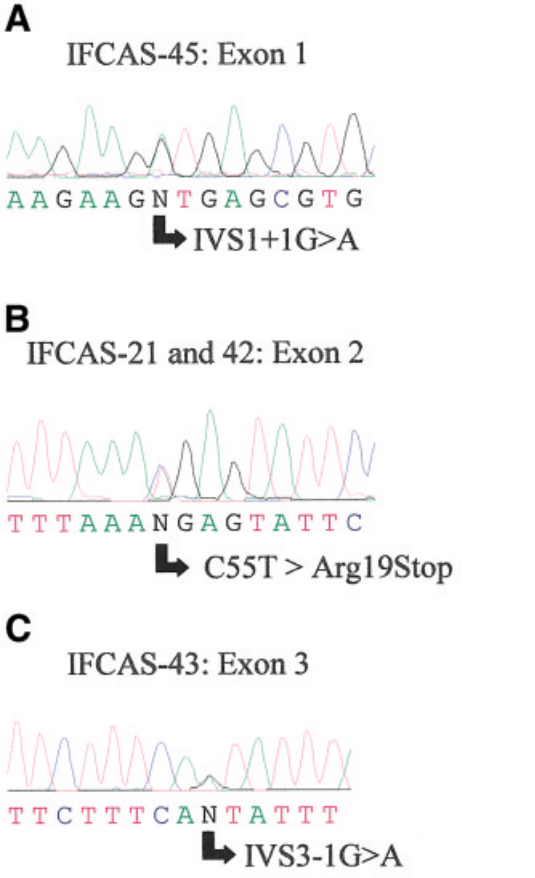

Fig. Sequence traces of CCM2 *mutations. (A) Invariant splice donor site mutation leading to a shortened protein with no phosphotyrosine-binding (PTB) domain. (B) A C to T transversion causing a nonsense mutation leading to degradation of the mRNA or to shortened protein with no PTB domain. (C) Invariant splice acceptor site mutation leading to deletion of exon 3 and part of the PTB domain. IFCAS = International Familial Cavernous Angioma Study.*

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Corrections

Li ST, Matsushita M, Moriwaki A, Saheki Y, Lu Y-F, Tomizawa K, Wu H-Y, Terada H, Matsui H. HIV-1 Tat inhibits long-term potentiation and attenuates spatial learning. Ann Neurol 2004;54:362-371 (March 2003).

The word "Tat" was missing from the title listed above as printed in the journal and posted online in Wiley Interscience. The corrected title is posted above.

The publisher regrets this oversight.

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Drost G, Verrips A, Hooijkaas H, Zwarts M. Glutamic acid decarboxylase antibodies in Satoyoshi syndrome. Ann Neurol 2004;54:450-451 (March 2003).

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