

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

Luanne M. Metz, MD, FRCPC,¹ Yunyan Zhang, MD,² Michael Yeung, MD, FRCPC,¹ David G. Patry, MD, FRCPC,¹ Robert B. Bell, MD, FRCPC,¹ Cristina A. Stoian, MD, MSc,¹ V. Wee Yong, PhD,¹ Scott B. Patten, MD, PhD,³ Pierre Duquette, MD, FRCPC,⁵ Jack P. Antel, MD, FRCPC,⁶ and J. Ross Mitchell, PhD^{1,2,4}

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

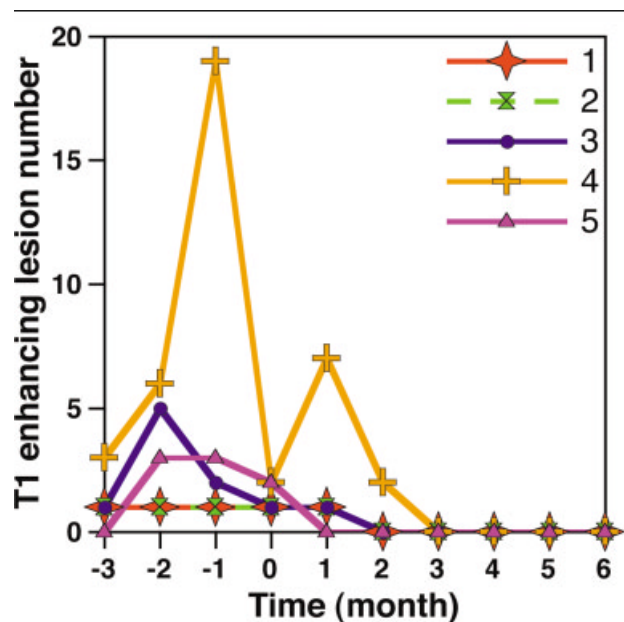


Fig. T1-enhancing lesion number from the magnetic resonance imaging scans of the five patients that exhibited enhancing lesions.

limit conclusions, but reduced MRI activity is encouraging and calls for definitive studies to establish minocycline efficacy in MS.

This study was funded by an Interdisciplinary Health Research Team grant of the Canadian Institute of Health Research (CRT 43824, L.M.M., N.M.Y., S.B.P., P.D., J.P.A., J.R.M.).

Departments of ¹Clinical Neurosciences, ²Seaman Family MR Research Centre, ³Community Health Sciences and Psychiatry, and ⁴Diagnostic Imaging, University of Calgary, Calgary, Alberta; and ⁵Department of Neurology, University of Montreal; and ⁶Department of Neurology, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada

References

- Brundula V, Rewcastle NB, Metz LM, et al. Targeting leukocyte MMPs and transmigration: minocycline as a potential therapy for multiple sclerosis. *Brain* 2002;125:1297–1308.
- Popovic N, Schubart A, Goetz BD, et al. Inhibition of autoimmune encephalomyelitis by a tetracycline. *Ann Neurol* 2002;51: 215–223.
- Wells J, Hurlbert J, Fehlings M, Yong VW. Neuroprotection by minocycline facilitates significant recovery from spinal cord injury. *Brain* 2003;126:1628–1637.

DOI: 10.1002/ana.20111

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

Dominique J. Verlaan, BSc,¹ Sandra B. Laurent, BTS,¹ Daniel L. Rochefort, MSc,¹ Christina L. Liquori, BS,² Douglas A. Marchuk, PhD,² Adrian M. Siegel, MD,³ and Guy A. Rouleau, MD, PhD⁴

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 reported⁴). 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.

D.J.V. is supported by an Quebec Health Research Fund Training and Support for Research (FRSQ-FCAR) scholarship. G.A.R. is supported by the CIHR and the Quebec Health Research Fund (FRSQ).

We thank the patients and the physicians for their participation in this study.

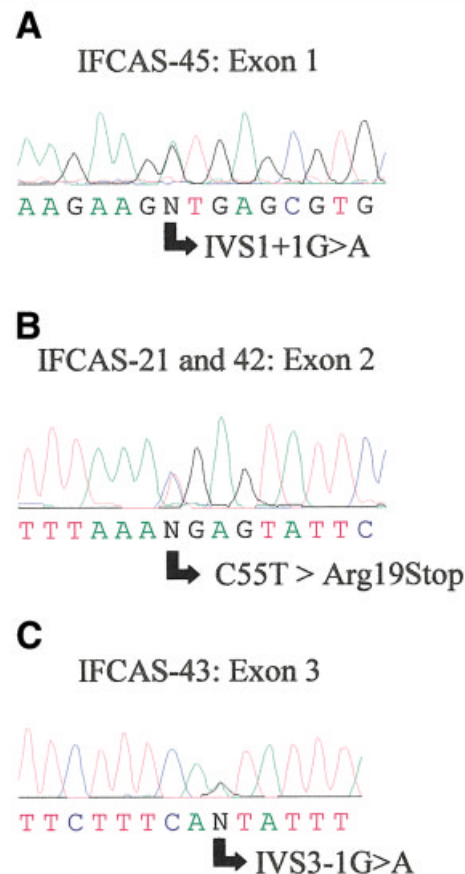


Fig. Sequence traces of *CCM2* mutations. (A) Invariant splice donor site mutation leading to a shortened protein with no phosphotyrosine-binding (PTB) domain. (B) A C to T transversion causing a nonsense mutation leading to degradation of the mRNA or to shortened protein with no PTB domain. (C) Invariant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

¹Center for Research in Neurosciences and Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada; ²Department of Molecular Genetics and Microbiology, Duke University Medical Center, Durham, NC; ³Epilepsy Program, Department of Neurology, University Hospital, Zürich, Switzerland; and ⁴Center for Research in Neurosciences, Montreal General Hospital and Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada

References

- Russell DS, Rubenstein LJ. Pathology of tumors of the nervous system. In: Edition T, ed. Baltimore: Williams and Wilkins, 1989:730–736.
- Rigamonti D, Hadley MN, Drayer BP, et al. Cerebral cavernous malformations: incidence and familial occurrence. *N Engl J Med* 1988;319:343–347.
- Siegel AM, Andermann E, Badhwar A, et al. Anticipation in familial cavernous angioma: a study of 52 families from International Familial Cavernous Angioma Study. *Lancet* 1998;352:1676–1677.

4. Liquori LL, Berg MJ, Siegel AM, et al. Mutations in a gene encoding a novel protein containing a phosphotyrosine-binding domain cause type 2 cerebral cavernous malformations. *Am J Hum Genet* 2003;73:1459–1464.
5. Verlaan DJ, Davenport WJ, Stefan H, et al. Cerebral cavernous malformations: mutations in *Krit1*. *Neurology* 2002;58: 853–857.

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.

DOI: 10.1002/ana.20019

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

In the HTML version of this article, posted online at www.interscience.wiley.com, DOI 10.1002/ana.20007, affiliation number 2 should read:

Department of Clinical Neurophysiology, Institute of Neurology, University, Medical Centre Nijmegen, Nijmegen, The Netherlands

The affiliations are listed correctly in the print and online PDF versions.

The publisher regrets this oversight.

DOI: 10.1002/ana.20114