

# Minocycline Impedes the Evolution of Gd-enhancing Lesions into Black Holes in Patients with Multiple Sclerosis

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## Introduction

New lesions in multiple sclerosis (MS) are commonly initiated with perivascular inflammation, followed by focal blood brain barrier (BBB) damage. Such pathological changes can be reflected as enhancement on post-contrast T1-weighted (T1w) MRI, accompanied by hyperintensity on T2-weighted (T2w) MRI. At this stage, the lesions appear either hypointense or isointense on the corresponding pre-contrast T1w MRI. It has been shown that 38% of the new MS lesions evolve into persistent hypointense lesions ('black holes') after five months.<sup>1</sup> Black holes represent severe and irreversible axon and myelin loss.<sup>2</sup> Strong correlations have been found between black holes and patient disability in MS.<sup>3</sup> Minocycline has been shown to reduce the activity and formation of gadolinium (Gd)-enhancing lesions in a cross over MS trial.<sup>4</sup> However, the ability of minocycline to prevent the accumulation of severe tissue damage is unknown. Here we examine the impact of minocycline treatment on the evolution of Gd-enhancing lesions into black holes in MS over a 3-year period.

## Subjects and Method

Ten relapsing remitting MS patients (age 18 ~ 50 years, expanded disability status scale 1.5 ~ 5.5, disease duration 1 ~ 16 years) have been enrolled. 3T MRI was performed monthly from 3 months pretreatment to 6 months during treatment, then annually up to 36 months. The imaging protocol included a fast spin-echo (SE) T2w MRI (TR/TE = 2716/80 ms, FOV = 24 cm<sup>2</sup>, matrix size = 512 x512, slice thickness = 3 mm, no gap) and SE pre- and post-contrast (Gd 0.1 mmol/kg) T1w MRI (TR/TE = 650/8 ms). Gd-enhancing lesions were evaluated at their appearance for hypo- or isointensity on the T1w MRI. Each lesion with Gd-enhancement was further differentiated into 'new' or 'old' based on whether the lesion area was normal appearing white matter (NAWM) (new) or an existing lesion (old) on the T2w MRI acquired one month earlier. The evolution of each Gd-enhancing lesion was assessed on the subsequent scans for the presence of a black hole and the occurrence of re-enhancement on the corresponding T1w MRI. An experienced neuroradiologist completed the lesion evaluation process twice, separated by two weeks. An ANOVA was performed to assess lesion number difference between time points ( $\alpha = 0.05$  was deemed significant).

## Results

As previously reported,<sup>4</sup> 5/10 patients had active scans pretreatment. All patients completed months 6 study, but only eight completed months 36 scan. In total, 12 Gd-enhancing lesions were identified: 8 at baseline and 4 at month one after commencement of treatment. None of the identified lesions had reoccurrence of enhancement during follow up period. 6/12 lesions were T1-hypointense, and 6/12 were T1-isointense at the time of their appearance (Table). 3/12 lesions were assessed as new in this sample. None of them became black holes. There were 4 old T1-hypointense lesions, none of these lesions evolved into black holes. Of the 5 old T1-hypointense Gd-enhancing lesions, two changed to NAWM on the T1w MRI at months 6 and 36 respectively (Figure). Overall, by month 6 there were fewer black holes than at baseline ( $p < 0.05$ ). Also, by month 36 there were fewer black holes than at month 6 ( $p < 0.05$ ).

## Discussion and Conclusions

This small study shows that, in addition to suppressing Gd-enhancement, minocycline treatment impedes the evolution of Gd-enhancing lesions into black holes. This may be due to the rapid effect of minocycline down-regulating inflammation by inhibiting the secretion and activity of matrix metalloproteinase.<sup>5</sup> However, the recovery of Gd-enhancing hypointense T1 lesions to NAWM suggests that minocycline may also aid white matter repair. This is consistent with a previous study showing that minocycline is neuroprotective in a murine model of spinal cord injury.<sup>6</sup> Nonetheless, minocycline reduced significantly the formation of destructive black holes. Larger definitive trials are underway to confirm the therapeutic effect of minocycline in MS, its impact on other MRI-derived parameters, and their correlation with clinical indicators of disease status.

## References

1. Ciccarelli O, et al. *Eur J Neurol* 1999; 6: 455-459.
2. Bruck W, et al. *Ann Neurol* 1997; 42: 783-793.
3. Van Walderveen MAA, et al. *Ann Neurol* 1999; 46: 79-87.
4. Metz LM, et al. *Ann Neurol* 2004; 55: 756.
5. Brundula V, et al. *Brain*; 2002: 1297-1308.
6. Wells J et al. *Brain* 2003, 126: 1628-1637.

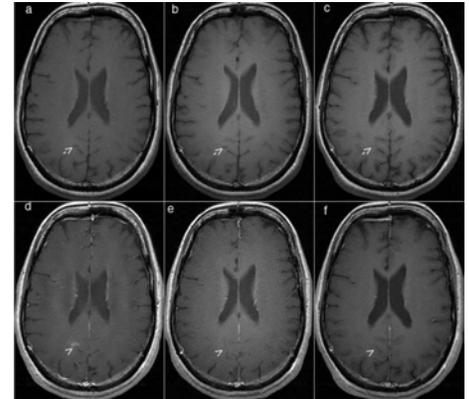


Figure. An 'old' Gd-enhancing lesion at baseline (d) showing hypointensity T1 (a). Black hole was smaller on M6 (b). It disappeared on M36 (c). No re-enhancement occurred after M1 (e,f).

Different time points	Lesion type				Total lesion #	
	New lesions		Old lesions		Gd+	Hypo-T1/ Holes
	Iso- T1	Hypo-T1	Iso-T1	Hypo-T1		
Baseline& M1	2	1	4	5	12	6
# of holes M6	0	0	0	4	0	4
# of holes M36	0	0	0	3	0	3

Iso(Hypo) = iso(hypo)intensity on T1w MRI; Gd+ = Gd-enhancing; Holes = black holes.