

## Short communication

## Brain magnetic resonance imaging in adults with asthma ☆☆☆

J. Parker<sup>a</sup>, L.J. Wolansky<sup>b</sup>, D. Khattry<sup>a</sup>, G.P. Geba<sup>a</sup>, N.A. Molfino<sup>a,\*</sup><sup>a</sup> MedImmune, LLC, One MedImmune Way, Gaithersburg, MD, 20878, United States<sup>b</sup> CoreLab Partners, 100 Overlook Center, Princeton, NJ, 08540, United States

## ARTICLE INFO

## Article history:

Received 29 April 2010

Accepted 14 September 2010

## Keywords:

Asthma

Magnetic resonance imaging

Brain

Lesion

Clinical study

## ABSTRACT

**Background:** In individuals with asthma, potential central nervous system changes can occur as a consequence of their asthma or therapy. Clinical trials of anti-asthmatic therapies might benefit from using magnetic resonance imaging (MRI) to assess potential brain abnormalities. **Purpose:** As part of the clinical safety evaluation of a monoclonal antibody directed against interleukin-9 for the treatment of asthma, we assessed whether brain MRI is an appropriate screening tool to evaluate potential neurotoxicity.

**Methods:** Brain MRIs were conducted as part of a prespecified safety evaluation in adults aged 19 to 47 years with mild to moderate asthma treated with either the investigational monoclonal antibody or placebo. An independent neuroradiologist performed a blinded review of brain MRI scans obtained at baseline before dosing and day 28 after dosing from two separate clinical studies.

**Results:** Fifteen brain MRI abnormalities were noted in 13 of 21 subjects with asthma (62%). Nonspecific deep white matter hyperintensities (24%), perivascular space (24%), and abnormal anatomic findings (14%) were noted either at baseline or follow-up. Only 8 of 21 subjects (38%) with asthma had normal brain MRI results.

**Conclusions:** The high rate of incidental brain MRI findings suggests that these abnormalities are relatively common in patients with asthma. Thus, brain MRI may not be an appropriate screening tool to evaluate potential neurotoxicity in subjects during routine clinical studies without a baseline examination. Due to artifacts simulating lesions, an experienced radiologist should interpret all brain MRI results.

© 2010 Elsevier Inc. All rights reserved.

## 1. Introduction

Asthma is a complex, multifactorial disease of the airways characterized by chronic airway inflammation, reversible

airway obstruction, excessive mucus production, and airway hyperresponsiveness. Novel medications, including immunomodulator monoclonal antibodies, are currently under development for the treatment of asthma. However, modulation of the immune system is not without risk. For example, progressive multifocal leukoencephalopathy has been reported after treatment with immunomodulators such as natalizumab [1–3], corticosteroids [4], and transplant drugs such as tacrolimus [5]. In individuals with asthma, potential central nervous system changes can occur as a consequence of their asthma [6,7] or therapy, including chronic corticosteroid exposure, theophylline, and long-term prednisone treatment [8–10]. Clinical trials of such anti-asthmatic compounds might benefit from a safety

☆ The study and manuscript were sponsored by MedImmune, LLC.

☆☆ Disclosure Statement: Drs. Parker, Khattry, and Molfino are employees of MedImmune, LLC. Dr. Geba is a former employee of MedImmune, LLC. Dr. Wolansky received research funding from MedImmune, LLC, for the conduct of this study.

\* Corresponding author. Tel.: +1 301 398 5807; fax: +1 301 398 8807.

E-mail addresses: [parkerj@medimmune.com](mailto:parkerj@medimmune.com) (J. Parker), [Wolansky@radpharm.com](mailto:Wolansky@radpharm.com) (L.J. Wolansky), [khattryd@medimmune.com](mailto:khattryd@medimmune.com) (D. Khattry), [gebagp@earthlink.net](mailto:gebagp@earthlink.net) (G.P. Geba), [molfino@medimmune.com](mailto:molfino@medimmune.com) (N.A. Molfino).

evaluation using magnetic resonance imaging (MRI) to assess potential brain abnormalities.

We examined brain MRI data from subjects with mild to moderate asthma enrolled in two early-phase clinical studies to examine the effects of an immunomodulator on asthma. The intent of this analysis was to assess whether brain MRI is an appropriate tool to monitor possible neurotoxicity in subjects with asymptomatic asthma during clinical studies. We report here the results of this investigation.

## 2. Methods

Subjects with mild to moderate asthma were selected from two early-phase studies of an investigational new monoclonal antibody directed against interleukin-9 for the treatment of asthma. Noncontrast MRI of the brain was obtained during the screening evaluation (predose) and 28 days after administration of study drug as part of a prespecified safety evaluation intended to determine whether neurotoxicity resulted from administration of the monoclonal antibody as compared with placebo. Subjects who had both baseline and follow-up brain MRI scans were included in the assessment. Noncontrast scans included T1, T2, diffusion-weighted, and FLAIR sequences. Post-contrast scans were obtained with T1-weighting.

On an ongoing basis, a neuroradiologist or general radiologist at each investigational site interpreted each brain MRI and reported the results to the study site. An independent neuroradiologist blinded to treatment and to the order of the studies subsequently performed a secondary review of all available brain MRI scans. In two cases, additional brain MRIs were conducted to determine the nature of a previously noted abnormality. One of the follow-up brain MRIs required gadolinium contrast to make an accurate diagnosis.

Baseline and periodic neurologic assessments were performed by the investigators on all subjects as part of the physical examinations.

Both studies were conducted in accordance with the Declaration of Helsinki and approved by an institutional review board/independent ethics committee. Written informed consent was obtained from each subject before study entry.

## 3. Results

Brain MRIs were available for 21 subjects at both baseline and 28-day follow-up evaluations. Nine subjects were male and 12 were female; the mean age was 29.2 years (SD = 8.62). Two subjects were African-American; all others were white. Fifteen brain MRI abnormalities were noted in 13 of 21 subjects (62%; Table 1). Nonspecific deep white matter hyperintensities (5 of 21 subjects; 24%), perivascular space (5 of 21 subjects; 24%), and abnormal anatomic findings (3 [Chiari malformation, coaptation of frontal horns, sinusitis] of 21 subjects; 14%) were noted either at baseline or follow-up. Eight of 21 subjects (38%) had a normal brain MRI scan at both baseline and day 28.

Brain MRI abnormalities were observed in 3 subjects (14%) at day 28 but not at baseline. None of these subjects exhibited neurologic symptoms or signs on day 28 or on

**Table 1**  
MRI assessment: lesions and abnormalities<sup>a</sup>.

Subjects		Brain MRI finding	Neurologic history	Psychiatric history
Age	Gender			
22	M	Perivascular space		
21	F	Perivascular space		
22	M	Perivascular space		Depression
39	F	Perivascular space <sup>b,c</sup> ; White matter hyperintensity	Migraine	
22	M	Perivascular space; White matter hyperintensity	Migraine	
38	F	White matter hyperintensity	Head injury	Depression
27	F	White matter hyperintensity	Migraine	Depression
37	F	White matter hyperintensity		Depression
26	M	Chiari malformation		
31	F	Coaptation of frontal horns		
47	F	Sinusitis		
39	F	Ghosting artifact <sup>b,d</sup>		Drug abuse
19	F	Geometric distortion artifact <sup>b,e</sup>	Syncope	
36	M	Normal	Migraine	
27	M	Normal		Depression
23	M	Normal	Migraine	
19	F	Normal		
23	F	Normal	Migraine	
19	M	Normal		Attention Deficit Disorder
37	F	Normal		
39	M	Normal		

<sup>a</sup> Unless noted otherwise, abnormalities were observed at both baseline and day-28 follow-up.

<sup>b</sup> Abnormality observed only at day 28.

<sup>c</sup> See Fig. 1A.

<sup>d</sup> See Fig. 1B.

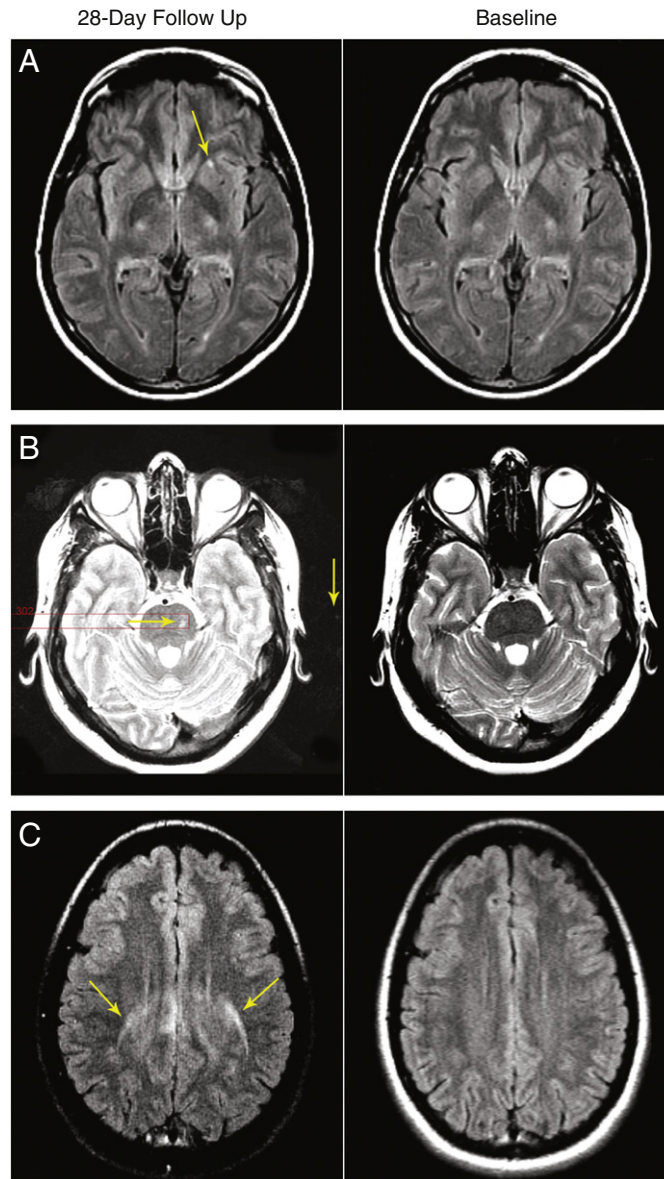
<sup>e</sup> See Fig. 1C.

follow-up evaluation. In 1 subject, a 39-year-old female, the finding resembled a typical large perivascular space (Fig. 1A). However, the head positioning of the two scans was not identical, predisposing the image to effects of partial volume averaging, which can render an abnormal structure invisible when sharing a pixel with adjacent normal tissue. This likely accounted for the structure's absence on the baseline scan. Use of standardized head positioning using an internal frame of reference such as a line drawn from the undersurface of the genu to the undersurface of the splenium can decrease this problem.

On the T2 images of the brainstem from another 39-year-old female subject, possible abnormalities were traced running in the vicinity of the pons (Fig. 1B). The location of the abnormalities paralleled the location of a vessel from image to image, which is typical for ghosting artifacts. A follow-up examination confirmed that this was an artifact.

In a third subject, a 19-year-old female, scattered bihemispheric punctate hyperintensities were reported by the site radiologist. However, upon central review by the neuroradiologist, bilateral magnetic susceptibility artifacts were noted (Fig. 1C); these were produced by the presence of ferromagnetic material related to the teeth (dental amalgam). These abnormalities were present at baseline but at a different anatomic level due to differences in the performance of the MRI.

No neurologic abnormalities were reported in any subject in the two studies during physical examinations.



**Fig. 1.** A, A large perivascular space on a brain MRI scan of a 39-year-old female. Scan at 28 days demonstrated a small hyperintensity typical of a prominent perivascular space, in terms of its basal ganglia location and its small size (arrow in 28-day scan). Scan at baseline did not demonstrate prominent perivascular space in left basal ganglia (baseline scan). The head positioning of the two scans was not identical, predisposing the image to effects of partial volume averaging. Partial volume averaging makes hyperintense foci  $\leq 3$  mm inconsistently imaged with routine 5 mm thick sections. B, Ghosting artifact in the vicinity of the pons on a brain MRI scan of a 39-year-old female. T2-weighted image at 28 days through pontine hyperintensity with special wide windows demonstrates replicas of the hyperintensity extending outside the subject, typical of “ghosting” or pulsation artifact (arrow in 28-day scan). Red rectangle demonstrates linear periodic nature of this artifact. A follow-up examination confirmed that this was an artifact. T2-weighted image at baseline did not demonstrate pontine hyperintensity (baseline scan). C, Geometric distortion artifact on a brain MRI scan of a 19-year-old female. Scan at 28 days demonstrated supratentorial hyperintensities bilaterally (arrows in 28-day scan), which were read by the site radiologist as pathological, but were unequivocally determined to be artifactual upon central review, representing geometric distortion due to ferromagnetic dental metal. Angular appearance and disregard of anatomic boundaries suggest an artifactual basis for this finding. Scan at baseline did not demonstrate the artifacts at the same anatomic level (baseline scan).

#### 4. Discussion

To our knowledge, this is the first assessment of brain MRI structural abnormalities in subjects with asthma. Stable brain MRI scans were expected over time due to the brief follow-up period in the studies; therefore, any on-study change would have raised safety concerns. The brain MRI scans of most

subjects were stable. Three on-study changes were observed, but these were attributed to artifacts or technical limitations of brain MRI.

A literature review of cross-sectional studies of healthy elderly volunteers revealed that between one third and two thirds of subjects older than 60 years had at least one white matter hyperintensity [11,12]. Based on a systematic review

and meta-analysis of 16 publications reporting data between 1989 and 2008, Morris et al. concluded that incidental findings on brain MRI are common, prevalence increases with age, and the findings are not sufficient to justify screening healthy asymptomatic people [13]. Even in pathologies such as bipolar disorder, where higher rates of white matter hyperintensities have been expected, studies have demonstrated that there was no association with higher rates of white matter hyperintensities compared with other psychiatric illnesses [14,15]. Another study found small brain MRI hyperintensities in the deep white matter of 34% of healthy subjects aged 44 to 48 years ( $N=428$ ) [16]. In a head-to-head comparison between normal control subjects and neuropsychiatric patients ( $N=641$ ; age range, 18 to 50 years), incidental finding rates were 31%, 43%, and 36% in patients, normal controls, and the total, respectively [17]. These values are consistent with the number of abnormalities described in this report, suggesting that routine analysis of these features by brain MRI may yield comparable results between asthma patients and healthy cohorts or patients with other diseases. Because we did not measure the volume of specific brain regions, the possibility that this may be used to distinguish asthma patients from healthy cohorts remains untested. A case of an asthma patient who had been treated with theophylline and subsequently developed acute encephalopathy with augmented oxidative stress and accompanying neuronal damage has been reported [9]. Nevertheless, abnormal brain MRI results must be interpreted cautiously. Furthermore, in addition to brain MRI, a comprehensive neurotoxicity safety assessment should incorporate periodic neurologic examinations and neuropsychiatric testing for mood disturbance and suicidal ideation.

In conclusion, the rate of incidental brain MRI findings in subjects with mild to moderate asthma observed in our studies provides a benchmark for asthma populations in general, and a younger cohort of patients with asthma in particular. The high rate of incidental brain MRI findings observed in our cohort and literature review suggests that these abnormalities are relatively common in healthy individuals and in individuals with different diseases, including subjects with asthma. In addition, technical limitations may generate artifacts, further limiting the use of brain MRI in studies.

The use of brain MRI may be warranted to screen for potential toxicity. This could be most valuable in situations where occult lesions are likely. In light of the high probability of incidental findings, baseline brain MRI scans would be required to identify the presence of new lesions. In a given subject, the scans should be carried out with identical MR units, pulse sequence parameters, and head positioning. It is also recommended that a radiologist with training and experience in the interpretation of brain MRIs should review all of the MRI scans to differentiate artifact from pathologic findings and to recommend appropriate follow-up assessments.

#### Author contributions

J.P., L.J.W., G.P.G., and N.A.M. were involved in the design of the study, analysis of the data, and interpretation of the results;

D.K. was involved in the analysis of the data and interpretation of the results; all authors critically reviewed and revised the manuscript and approved the final version. N.A.M. had full access to all of the study data and takes full responsibility for the integrity of all of the data and the accuracy of the data analysis.

#### Acknowledgments

The authors thank Michael L. Leski, PhD, EurAsia Medical Writers, and Miriam Gitler, PhD, MedImmune, LLC, for assistance with the preparation of the article.

#### References

- [1] Langer-Gould A, Atlas SW, Green AJ, Bollen AW, Pelletier D. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. *N Engl J Med* 2005;353(4):375–81.
- [2] Kleinschmidt-DeMasters BK, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. *N Engl J Med* 2005;353(4):369–74.
- [3] Van Assche G, Van Ranst M, Scot R, Dubois B, Vermeire S, Noman M, et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. *N Engl J Med* 2005;353(4):362–8.
- [4] Viallard JF, Lazaro E, Ellie E, Eimer S, Camou F, Caubet O, et al. Improvement of progressive multifocal leukoencephalopathy after cidofovir therapy in a patient with a destructive polyarthritis. *Infection* 2007;35(1):33–6.
- [5] Junna MR, Rabinstein AA. Tacrolimus induced leukoencephalopathy presenting with status epilepticus and prolonged coma. *J Neurol Neurosurg Psychiatry* 2007;78(12):1410–1.
- [6] Rosenkranz MA, Busse WW, Johnstone T, Swenson CA, Crisafi GM, Jackson MM, et al. Neural circuitry underlying the interaction between emotion and asthma symptom exacerbation. *Proc Natl Acad Sci USA* 2005;102(37):13319–24.
- [7] Rosenkranz MA, Davidson RJ. Affective neural circuitry and mind–body influences in asthma. *Neuroimage* 2009;47(3):972–80.
- [8] Brown ES, Woolston DJ, Frol AB. Amygdala volume in patients receiving chronic corticosteroid therapy. *Biol Psychiatry* 2008;63(7):705–9.
- [9] Shiihara T, Kato M, Ichihara T, Takahashi Y, Tanuma N, Miyata R, et al. Acute encephalopathy with refractory status epilepticus: bilateral mesial temporal and claustral lesions, associated with a peripheral marker of oxidative DNA damage. *J Neurol Sci* 2006;250(1–2):159–61.
- [10] Brown ES, Vera E, Frol AB, Woolston DJ, Johnson B. Effects of chronic prednisone therapy on mood and memory. *J Affect Disord* 2007;99(1–3):279–83.
- [11] Schmidt R, Petrovic K, Ropele S, Enzinger C, Fazekas F. Progression of leukoaraiosis and cognition. *Stroke* 2007;38(9):2619–25.
- [12] Spilt A, Geeraedts T, de Craen AJ, Westendorp RG, Blauw GJ, van Buchem MA. Age-related changes in normal-appearing brain tissue and white matter hyperintensities: more of the same or something else? *AJNR Am J Neuroradiol* 2005;26(4):725–9.
- [13] Morris Z, Whiteley WN, Longstreth WT Jr, Weber F, Lee YC, Tsushima Y, et al. Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ* 2009;339:b3016.
- [14] Breeze JL, Hesdorffer DC, Hong X, Frazier JA, Renshaw PF. Clinical significance of brain white matter hyperintensities in young adults with psychiatric illness. *Harv Rev Psychiatry* 2003;11(5):269–83.
- [15] Beyer JL, Young R, Kuchibhatla M, Krishnan KRR. Hyperintense MRI lesions in bipolar disorder: a meta-analysis and review. *Int Rev Psychiatry* 2009;21(4):394–409.
- [16] Wen W, Sachdev PS, Li JJ, Chen X, Anstey KJ. White matter hyperintensities in the forties: their prevalence and topography in an epidemiological sample aged 44–48. *Hum Brain Mapp* 2009;30(4):1155–67.
- [17] Royal JM, Peterson BS. The risks and benefits of searching for incidental findings in MRI research scans. *J Law Med Ethics* 2008;36(2):305–14, 212.