

# The Efficacy of Bisphosphonate to Increase the Skull Density Ratio of MRI-guided Focused Ultrasound Candidates with Brain Disorders

Hisashi Ito<sup>1,\*</sup>,  
Jordi Rumià<sup>2</sup>  
Shigeru Fukutake<sup>1</sup>,  
Kazuaki Yamamoto<sup>3</sup>,  
Toshio Yamaguchi<sup>4</sup>,  
Takaomi Taira<sup>5</sup> and  
Tetsumasa Kamei<sup>1</sup>

## Abstract

**Background:** Skull density ratio (SDR) is one of the key factors for the success of MRI-guided focused ultrasound (MRgFUS) treatment for brain diseases. We examined the efficacy of alendronate (Aln) to improve a SDR value.

**Materials and Methods:** The subjects were 6 Parkinson's disease patients (2 men, 4 women, 70.7 ± 7.7 years old) and 1 essential tremor patient (1 man, 81 years old). Despite of desire to MRgFUS treatment, we could not schedule their treatments because their SDR values were too low. As they coexisted with untreated osteoporosis, we administered 35 mg of Aln weekly and followed their SDR values every 3 months.

**Results:** The SDR value elevated in 4 patients following the administration of Aln and we could perform MRgFUS treatment successfully. No adverse reactions related with Aln were observed.

**Conclusion:** Although it will take several months, Aln may be a useful option for MRgFUS candidates with a low SDR value.

**Keywords:** Skull density ratio; Brain diseases; Parkinson's disease

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## Introduction

Transcranial MRI-guided focused ultrasound (MRgFUS) is a novel neurosurgical tool based on the technology by Fry brothers [1]. It consists of high intensity ultrasound for ablation, MR imaging for confirming target location, and MR thermography for real-time monitoring of thermal process. Compared to previous neurosurgical interventions, MRgFUS is characterized with minimum invasiveness as it requires neither burr hole opening nor device implantation. MRgFUS has been applied for several neurological or psychological disorders, including Parkinson's disease (PD) and essential tremor (ET) [2-8]. There are two key factors determining the success of MRgFUS treatment for brain diseases: the skull volume and skull density ratio (SDR) [9]. Here we report a preliminary research on the efficacy of alendronate (Aln), one of the popular bisphosphonates for osteoporosis, to elevate the SDR value in patients of PD and ET.

## Materials and Methods

This is a preliminary, open labeled and retrospective study whose objects were 6 PD patients (2 men, 4 women, 70.7 ± 7.7 years old)

- 1 Department of Neurology, Shonan Fujisawa Tokushukai Hospital, Fujisawa, Japan
- 2 Department of Functional Neurosurgery, ResoFUS ALOMAR Barcelona, University of Barcelona, Barcelona, Spain
- 3 Department of Neurosurgery, Shonan Kamakura General Hospital, Kamakura, Japan
- 4 Research Institute of Diagnostic Imaging, Shin-Yurigaoka General Hospital, Kawasaki, Japan
- 5 Department of Neurosurgery, Tokyo Women's Medical University, Tokyo, Japan

### \*Corresponding author:

Dr. Hisashi Ito

✉ hisashi.ito@tokushukai.jp

Department of Neurology, Shonan Fujisawa Tokushukai Hospital, 251-0041, Fujisawa, Japan.

**Tel:** +81-466-35-1177

**Fax:** +81-466-35-1300

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and 1 ET patient (1 man, 81 years old). Demography of patients was shown in the **Table 1**. All the patients desired to perform MRgFUS treatment, which had been approved by the Review Board of Tokushukai Medical Alliance or University of Barcelona. They provided a written informed consent in accordance with the Declaration of Helsinki before treatment commenced. However, we had to suspend their treatments because of low SDR values (exclusion criteria: ≤ 0.30 in Japan, ≤ 0.40 in EU). As they had

**Table 1** Demography of patients.

No.	Age	Gender	SDR at baseline	Site	Disease	Target
1	56	M	0.35	UB	PD	Vim
2	78	F	0.26	SFTH	PD	GPI
3	80	M	0.25	SFTH	ET	Vim
4	70	F	0.24	SFTH	PD	GPI
5	72	F	0.29	SFTH	PD	Vim
6	75	F	0.29	SFTH	PD	Vim
7	73	M	0.27	SFTH	PD	Vim

UB: University of Barcelona; SFTH: Shonan Fujisawa Tokushukai Hospital

untreated osteoporosis diagnosed with a standard examination, we administered Aln 35 mg weekly and examined their SDR values every 3 months.

## Results

We followed the patients for 3 to 9 months of the administration of Aln. The SDR value is elevated gradually in 4 patients, though it reached a plateau in 2 patients (**Figure 1**). For these patients, we performed MRgFUS Vim thalamotomy or GPI pallidotomy and archived good outcomes [7]. We did not observe Aln-related adverse reactions at all.

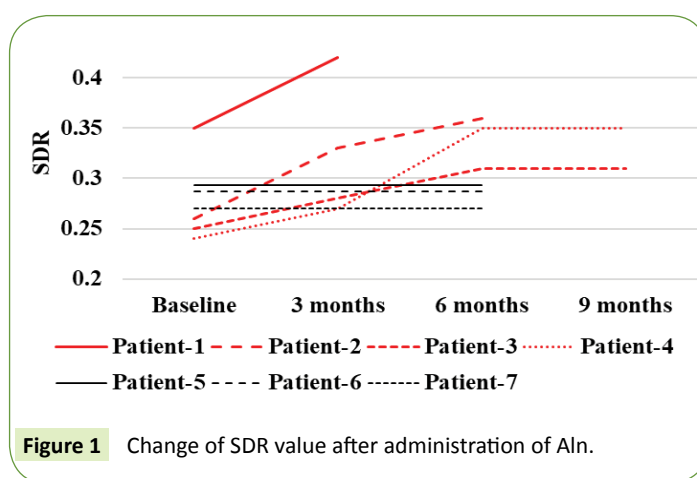
## Discussion

Transcranial MRgFUS is an innovative technology for several psychological and neurological disorders including PD and ET. The main advantages of MRgFUS are minimum invasiveness and the immediate onset of therapeutic effect. Most of the adverse events are mild and transient [2,5-8]. The primary therapeutic targets for PD and ET are ventral intermediate nucleus (Vim) for tremor [3,4,6] and globus pallidus internus (GPI) for motor-fluctuations [7,8]. In addition, the effectiveness and safety of pallidothalamic tractotomy for tremor and dyskinesia had been reported [5].

The skull is a marked barrier to ultrasonic energy transmission. SDR, the mean value for the ratio of Hounsfield units of marrow and cortical bone, which reflects the amount of ultrasonic energy that can penetrate the skull effectively, is one of the key factors needed to be taken into consideration for a successful MRgFUS procedure for brain disorders, and it shows a positive correlation with maximal temperature in the target lesion [9]. Therefore, optimizing a SDR value may be useful for MRgFUS candidates with a low SDR value, and it might be helpful to expand the patients indicated for MRgFUS.

Moreover, ultrasound elements tend to have a high incident angle with the skull and the number of elements which deliver energy effectively to the target is limited in MRgFUS GPI pallidotomy compared with Vim thalamotomy or pallidothalamic tractotomy because the GPI target locates laterally. Thus, high SDR value is critical especially in MRgFUS GPI pallidotomy. However, the appropriate method to elevate a SDR value has yet to be elucidated.

Aln is one of the third-generation bisphosphonates. Although the



**Figure 1** Change of SDR value after administration of Aln.

association between SDR and osteoporosis is not clear, Aln was previously reported to increase the degree and uniformity of bone matrix mineralization and decrease the porosity of cortical bone [10]. Aln could be a useful option for MRgFUS candidates with a low SDR value; however, the presence of non-responders and two patients reaching a plateau indicates the limitation of the efficacy of Aln and we have to consider that it takes several months for achieving enough value of SDR. In addition, bisphosphonates other than Aln, RANKL inhibitor, and recombinant human parathyroid hormone might have some potential to impact positively on a SDR value. Further investigations concerning the efficacy of Aln and other drugs for optimizing a SDR value are necessary.

## Conclusion

Aln could elevate a SDR value in some MRgFUS candidates with brain disorders.

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## Conflict of Interest

There are no conflicts.

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