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Short communication

Efficacy and safety of deferiprone for the treatment of pantothenate kinase-associated neurodegeneration (PKAN) and neurodegeneration with brain iron accumulation (NBIA): Results from a four years follow-up

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ABSTRACT

Objective: To evaluate the long-term effect of Deferiprone (DFP) in reducing brain iron overload and improving neurological manifestations in patients with NBIA.
Methods: 6 NBIA patients (5 with genetically confirmed PKAN), received DFP solution at 15 mg/kg po bid. They were assessed by UPDRS/III and UDRS scales and blinded video rating, performed at baseline and every six months. All patients underwent brain MRI at baseline and during follow up. Quantitative assessment of brain iron was performed with T2* relaxometry, using a gradient multi-echo T2* sequence.
Results: After 48 months of treatment clinical rating scales and blinded video rating indicated a stabilization in motor symptoms in 5/6 Pts. In the same subjects MRI evaluation showed reduced hypointensity in the globus pallidus (GP); quantitative assessment confirmed a significant increment in the T2* value, and hence reduction of the iron content of the GP.
Conclusion: The data from our 4-years follow-up study confirm the safety of DFP as a chelator agent for iron accumulation. The clinical stabilization observed in 5/6 of our patients suggests that DFP may be a reasonable therapeutic option for the treatment of the neurological manifestations linked with iron accumulation and neurodegeneration, especially in adult patients at early stage of the disease.
(Clinicaltrials.gov identifier: NTC00907283).

Deferiprone (DFP) is an oral active bidentate iron chelator effective in the lowering of intracellular iron. Its use is authorized for the treatment of iron overload in patients affected by thalassemia major (not suitable for deferoxamine). Its chemical–physical characteristics (low molecular weight, favorable octanol/water partition coefficient, neutral charge) guarantee good drug permeability through the blood–brain barrier [1].

NBIA (Neurodegeneration with Brain Iron Accumulation) is a class of neurodegenerative diseases that features a prominent extrapyramidal movement disorder, intellectual deterioration, and a characteristic deposition of iron in the basal ganglia [2,3]. PKAN (NBIA subtype 1) is the most common of NBIA with a typical MRI finding (the pallidal "eye-of-the-tiger sign"). While there is currently no cure for PKAN, promising researches offer new perspectives of treatment. The results of our previous one-year-treatment study [4,5] suggested that DFP might be effective in

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Table 1
Clinical and genetical data of the patients.

Patient	Sex	Age (years)	Disease Duration (years)	Clinical features	Diagnosis	MRI	Follow-up (months)
1	M	52	7	Cranial dystonia parkinsonism	NBIA	T2* hypointensities in GP (bilateral)	48
2	F	29	6	Multifocal dystonia	PKAN (Pank2 +)	T2* hypointensities in GP (bilateral) "tiger eye"	48
3	M	34	14	Multifocal dystonia parkinsonism	PKAN (Pank2 +)	T2* hypointensities in GP (bilateral) "tiger eye"	48
4	F	32	16	Multifocal dystonia parkinsonism	PKAN (Pank2 +)	T2* hypointensities in GP (bilateral) "tiger eye"	48
5	F	22	11	Multifocal dystonia parkinsonism	PKAN (Pank2 +)	T2* hypointensities in GP (bilateral) "tiger eye"	48
6	F	40	27	Multifocal dystonia parkinsonism retinitis pigmentosa	PKAN (Pank2 +)	T2* hypointensities in GP (bilateral) "tiger eye"	36

reverse iron deposition and improve neurological manifestations in patients with NBIA.

Due to these encouraging results we extended the treatment period. Here we report the clinical and neuroradiological findings of 6 patients (5 with genetically confirmed PKAN). Five completed 4 years of treatment, one received DFP for three years.

1. Patients and methods

After the conclusion of the first one-year pilot study [5] the participants were invited to join an extension study (2009–2012) for an additional three-year follow-up treatment. 5 out of 6 patients accepted and have been currently in treatment since 2008. One additional patient (Pt. 6) was enrolled later (2009) in the present study and recently completed 36 months of treatment. The extension trial was approved by the E.O. Ospedali Galliera Ethics Committee and the local Ethics Committee at the Cagliari center. All participants gave written informed consent.

All 6 patients included in this report (5 with genetically confirmed PKAN, 1 with idiopathic NBIA; Table 1) received DFP solution (Apopharm, Toronto, ON, Canada) at 15 mg/kg po bid. For inclusion criteria, procedures and safety monitoring see Ref. [4].

Follow-up visits were performed every six months. All patients were videotaped and assessed by neurologists expert in movement disorders from the Department of Neurosciences (University of Genoa) and from the Department of Neurology (Brotzu Hospital of Cagliari). The Unified Parkinson's Disease Rating Scale (UPDRS/III – Motor Section) and the Unified Dystonia Rating Scale (UDRS) were administered at baseline and during follow up. An independent neurologist made a blinded evaluation of the videotapes.

2. Magnetic resonance imaging

All patients underwent brain MRI at baseline and every 12 months during follow up. MRI examinations were carried out on a 1.5 T Sigma unit (GE Medical Systems, Milwaukee, WI) using a phased array head coil. The protocol included sequences for morphologic and quantitative assessment.

Quantitative assessment of brain iron was performed with T2* relaxometry, using a gradient multi-echo T2* sequence (field of view 24 cm, 255 × 224 matrix, slice thickness 5 mm, gap 3 mm, TR: 400 ms, 10 echoes at TE from 3.5 ms to 54 ms, flip angle 50°, acquisition time 4 min) to acquire each axial brain slice at ten echo time. Quantitative T2* maps were calculated off-line using a custom made reconstruction algorithm (FuncTool v. 5.2.09, GE Medical Systems).

Two oval ROI (10 mm^2) were manually drawn by a single neuroradiologist within the boundaries of the right and left globus pallidus at different levels, on consecutive sections. The signal intensity was measured at each echo time. The final T2* value was the mean of the results determined for each level.

As internal control, several (2 or more, depending on the size of the region) circular ROIs of 24 mm^2 were drawn in the white matter of cerebral and cerebellar hemispheres, where iron concentration is assumed to be low, and in thalamic nuclei.

In order to determine the reproducibility of the quantitative measurement in the two centers, a study of a phantom containing samples of known different concentrations of iron was performed in Cagliari and Genoa.

3. Results

3.1. Clinical changes

Clinical rating scales demonstrated an improvement or a stabilization of symptoms (according to both clinical scores and blinded video rating) in 3 patients (Pts. 1,4,6). Two patients (Pts. 2,3) were judged as mild worsened by the blinded video raters but the clinical scores were unchanged or mild improved. Only one patient (Pt. 5) was assessed as definitively worsened by both clinical scores and blinded video evaluation (Table 2).

For 2 patients (Pts. 3,4) we have additional information as their video and clinical data are available from 2004 (time of diagnosis), that is 4 years before the treatment onset. Clinical scales (Fig. 1) clearly show a difference in the rate of symptoms progression before and after 2008 (time of treatment onset).

About the MRI results (Table 2), a long term reduction (Pts. 2,3,4,6) or stabilization (Pt. 1) of pallidal iron overload was observed in the large majority of the patients. Multiparametric T2* brain MRI images of Pt. 2. (Fig. 2), only given as an example, shows the

Table 2
Clinical (rating scales and video rating) and radiological findings (MRI) of the patients at baseline and during the follow-up (24 and 48 months).

Patient	UPDRS motor score			UDRS global score			Blinded video rating		MRI T2*weighted GE values in GPi (ms)		
	Basal	24	48	Basal	24	48	24	48	Basal (R–L)	24 (R–L)	48 (R–L)
1	13	6	13	5	4	4	Improved moderately	Improved moderately	–	54–42	50–49
2	13	9	9	5	6	6	Mild worsening	Unchanged	23–25	30–30	30–35
3	29	21	23	13	13	13	Mild worsening	Mild worsening	19–21	22–20	23–25
4	47	43	47	21	21	22	Unchanged	Unchanged	20–20	23–25	24–25
5	31	34	39	16	24	54	Worsened	Worsened	–	22–26	14–13
6	25	21	20 (36 mo)	30	28	27 (36 mo)	Unchanged	Unchanged (36 mo)	21–18	37–42	42–44 (36 mo)