Neurological Sciences (2019) 40:1357–1361
https://doi.org/10.1007/s10072-019-03847-x

ORIGINAL ARTICLE

Efficacy and safety of deferiprone for the treatment of superficial siderosis: results from a long-term observational study

Giovanni Cossu[1] · Giovanni Abbruzzese[2,3] · Gian Luca Forni[4] · Gildo Matta[5] · Valeria Pinto[4] · Uberto Ruffinengo[6] · Valentina Oppo[1] · Roberta Marchese[2,3]

Received: 19 October 2018 / Accepted: 13 March 2019 / Published online: 22 March 2019

Abstract

Background Superficial siderosis (SS) of the central nervous system is a rare and heterogeneous condition due to deposition of hemosiderin on the surface of the brain and spinal cord. The usually progressive clinical course is characterized by a combination of hearing loss, cerebellar ataxia, and myelopathy. There is no known treatment for SS, but the iron chelator deferiprone (DFP) has been proposed as a potentially useful treatment.

Methods We present a long-term (average 3.7 years) evaluation of four cases of SS treated with DFP (15 mg/kg po bid).

Results Treatment with DFP proved safe and well tolerated. Two out of the four subjects were unchanged while the other two presented a clinical improvement with reduction of postural instability and cerebellar signs. Blinded evaluation of magnetic resonance imaging (performed every 6 months during follow-up) showed a reduction of the abnormal iron deposition for all patients.

Conclusions This long-term observational study suggests that DFP may be effective in the management of the neurological manifestations associated with iron accumulation in SS.

Clinicaltrials.gov identifier NTC00907283

Keywords Superficial siderosis · Iron accumulation · Deferiprone · Magnetic resonance imaging

Introduction

Superficial siderosis (SS) of the central nervous system is a clinical syndrome due to deposition of hemosiderin on the surface of the brain and spinal cord because of recurrent bleeding in the subarachnoid space [1, 2]. It is a rare condition with a heterogeneous etiology (diseases of the dura mater, tumors, arteriovenous malformations, trauma, and surgical procedures) [1, 2], but the advent of magnetic resonance imaging (MRI) has increased the possibility of its identification.

The deposition of hemosiderin on the pial surface induces intracellular uptake of iron by glial cells that triggers gliosis, fibrosis, and neuronal damage with involvement of the cerebellum, brainstem, cranial nerves, and medulla. The progressive clinical features are usually characterized by a combination of hearing loss, cerebellar ataxia, and myelopathy, but other manifestations are possible. There is no known treatment for SS. Eliminating the cause of recurrent subarachnoid bleeding is rarely effective [3], and initial attempts to chelate the iron deposits showed no benefit [4, 5].

Deferiprone (DFP) is an oral active bidentate iron chelator effective in lowering intracellular iron, and its chemical-physical characteristics (low molecular weight, favorable octanol/water partition coefficient, and neutral charge) guarantee good drug permeability through the blood-brain barrier [6]. The efficacy of DFP has been investigated in patients presenting neurodegeneration with

✉ Giovanni Cossu
giovannicossu@aob.it

1 Neurology Service and Stroke Unit, Department of Neuroscience, AO Brotzu, P.le Ricchi, 1, 09134 Cagliari, Italy

2 Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics and Maternal and Child Health, University of Genova, Genoa, Italy

3 IRCCS Ospedale Policlinico San Martino, Genoa, Italy

4 Center for Congenital Anemias and Iron Dysmetabolism, Galliera Hospital, Genoa, Italy

5 Department of Radiology, G. Brotzu General Hospital, Cagliari, Italy

6 Neuroradiology Unit, Galliera Hospital, Genoa, Italy

brain iron accumulation (NBIA) [7, 8] as well as in Friedreich ataxia [9].

After its introduction, the safety and therapeutic efficacy of DFP were tested in single cases of patients with SS [10, 11], and a pilot study [12], over a 90-day period, showed that DFP was well tolerated and induced a reduction in hemosiderin deposition in some subjects. One case followed up for more than 3 years presented clinical resolution of hearing loss and ataxia [11]. Recently Kessler et al. [13] performed a long-term (2 years) prospective study of the effects of DFP treatment in 38 subjects with SS. MRI quantification demonstrated, in half of the patients, a reduction of hemosiderin that correlated with clinical stabilization.

Here, we present the clinical and neuroradiological (MRI) evaluation of four cases of SS treated with DFP and followed up to five (average 3.7) years.

Patients and methods

The clinical data of the four patients enrolled in the study are reported in Table 1. Subjects were assessed every 6 months by two neurologists expert in movement disorders from the Department of Neurosciences (University of Genoa).

Two expert neuroradiologists performed quantitative and qualitative analysis of iron accumulation changes: baseline MRI images were compared with the scans performed during the follow-up period (1–5 years post-drug).

The trial was approved by the E.O. Ospedali Galliera Ethics Committee, and all participants gave written informed consent before entering the study (Clinicaltrials.gov identifier: NTC00907283).

Treatment procedures

Patients received DFP solution (ApoPharma, Toronto, ON, Canada) at 15 mg/kg po bid, prescribed and monitored by the Microcitemia Center of E.O. Ospedali Galliera in Genoa. To reduce the risk of possible drug interference with hematologic homeostasis, we used a lower dose than is normally administered in patients with systemic iron overload (75 mg/kg per day) [7]. During the trial, we monitored safety and tolerability of the drug by measuring hemochrome (with leukocyte formula count) weekly and iron serum, ferritin, transferrin, creatinine, blood urea nitrogen (BUN), AST, ALT, calcium, phosphorous, protein electrophoresis, total proteins, and zinc levels monthly.

Magnetic resonance imaging

All patients underwent brain MRI at baseline and at every 6 months during follow-up. The protocol included sequences for morphologic and quantitative assessment. Images were acquired on a 1.5 T MRI.

For morphological and qualitative analysis, the protocol used included multiplane DWI, T1, FLAIR, T2*, and T2 sequences (T2 parameter: TR 9000, TE 126, FOV 24 cm, FA 90°, slice thickness 4 mm, gap 1 mm, matrix 256 × 256).

Two independent, experienced, blinded neuroradiologists reviewed the MRI scans to provide a qualitative evaluation based on appropriate analysis of the typical region of iron accumulation: surface of the brain, cerebellum, and spinal cord.

Given the impossibility of performing a standard iron load quantitative analysis by sampling specific region of interest (ROI), we applied an alternative method as proposed by Levy and Llinas in their recently published series of cases [12]. The MRI iron susceptibility signal at baseline was compared with post-drug scans. Three-dimensional images of the whole brain were rendered using OsiriX software (version 8.0; Pixmeo SARL, Geneva, Switzerland), and the total T2 signal was averaged and standardized to the maximum T2 signal of the cerebrospinal fluid in the lateral ventricles. Lower average T2 signals indicate increased hemosiderosis while higher T2 signals indicate less hemosiderosis [12].

Results

The four patients enrolled were males with an average age of 64.2 years (range 48–74 years). Although the etiology was variable (see Table 1), the clinical features included hearing loss, cerebellar ataxia, and pyramidal signs in all the subjects. Before entering the study, patients presented a slowly progressive course, and the average duration of disease before treatment was 7.7 year (range 4–11 years).

MRI is documented in all the patients striking hypointensity on T2-weighted sequences along the surface of the brain (mainly involving the brainstem and cerebellum) and of the spinal cord, consistent with the diagnosis of SS (see Table 2).

Clinical outcome

In the course of treatment with DFP, two patients (cases 1 and 4) did not show significant modifications of the neurologic examination and were subjectively stable; the other two subjects (cases 2 and 3) presented a clinical improvement with reduction of postural instability (and falls), incoordination, and dysarthria. They reported feeling subjectively improved and with increased autonomy. It is noticeable, in these two patients, that the treatment started in the shortest interval from the time of diagnosis; the clinical improvement occurred at least 1 year after the beginning of treatment in both subjects. No patient has reported fatigue.

Table 1 Clinical features of the patients

Subject	Age (years)	Gender	Etiology	Duration (years)*	Symptoms	Observation (months)	Clinical outcome
1	68	M	Unknown	10	Cerebellar ataxia with dysarthria and nystagmus (2004) Paraparesis with bilateral hyperreflexia and Babinski sign (2004) Positive Romberg sign (2004) Hearing loss (2011)	12	Unchanged
2	68	M	Idiopathic	6	Hearing loss (2008) Cerebellar ataxia with dysarthria and nystagmus (2011) Paraparesis with bilateral hyperreflexia and Babinski sign (2011) Retropulsion (2011)	48	Improved
3	74	M	Chronic liver disease (HBV-related) and head injury	4	Hearing loss (2007) Gait ataxia with dysarthria and falls (2008) Hyperreflexia (2008) Positive Romberg sign (2008)	60	Improved
4	48	M	Paragangliomatosis of the brain and spinal cord (with surgical removal and radiometabolic treatment)	11	Hearing loss (2003) Axial ataxia with retropulsion (2003) Hyperreflexia (2003)	28	Unchanged

*Time since first symptom

Treatment with DFP proved safe and well tolerated. No side effects were reported by the patients during the observation period. Laboratory investigations did not reveal any treatment-related abnormalities (including no changes in the blood cell count), and iron supplementation was not required.

MRI findings

Blinded evaluation by two neuroradiologists showed agreement in the identification of lesser extent of the abnormal iron deposition in the typical region of iron accumulation (surface of the brain, cerebellum, and spinal cord) at follow-up for all patients (Table 2).

In order to quantitatively evaluate brain iron load, comparison of the pre-treatment and post-treatment MRI parameters was performed to identify pairs of scans with the same echo time and the same captured brain volume. Three out of the four patients met these parameters and were suitable for the analysis.

The MRI quantitative analysis was performed for patient 1 at 1 year and for patients 2 and 4 at 2 years. In all cases, at

Table 2 MRI findings of the patients

Subject	Baseline (before treatment)	Blinded MRI rating after DFP treatment					
		6 months	12 months	24 months	36 months	48 months	60 months
1	T2-weighted hypointensities along the surface of the brainstem, cerebellum, globus pallidus (bilaterally), and spinal cord (total) Leukoencephalopathy and cerebellar atrophy	Unchanged	Improved	–	–	–	–
2	T2-weighted hypointensities along the surface of the brainstem, cerebellum, and spinal cord (total) Vascular gliosis	Siderosis unchanged; two new ischemic lesions	Unchanged	Improved	Unchanged	Improved	–
3	T2-weighted hypointensities along the surface of the brainstem, cerebellum (hemispheres and vermis), and spinal cord (total) Atrophy and gliosis (nucleo-capsular in the right hemisphere)	Unchanged	Unchanged	Improved	Unchanged	Improved	Improved
4	T2-weighted hypointensities along the surface of the cortex, brainstem, cerebellum, and spinal cord (C7-D1 and conus)	Unchanged	Improved	Unchanged	–	–	–

follow-up, an increased total T2 signal averaged and standardized to the maximum T2 signal of the cerebrospinal fluid in the lateral ventricles (Table 3) was detected, consistent with reduction in the total brain iron load.

Discussion

SS is an uncommon pathology characterized by a marked heterogeneity in etiopathogenesis and clinical outcome. For this reason, the published case series are rare and even rarer the references to systematic therapeutic approaches and long-term prognosis.

In the few works published previously on the topic, DFP proved to be well tolerated and effective in lowering CNS iron (as measured by MRI quantitative and qualitative analysis), but its ability to determine a clinical benefit is still debated. The main causes of this uncertainty consist of the infrequency of SS (which does not allow to design large placebo-controlled studies), its heterogeneous pathogenesis, and the brief period of treatment so far considered. It can be considered that longer observation time is needed to detect the treatment effectiveness in reverse or halting symptoms, also taking into account the variability of the natural history of the SS spectrum of illnesses.

With this goal in mind, we monitored for a long time the effect of DFP in a cohort of four patients with SS with slow progression, hearing loss, ataxia, and pyramidalism as the main clinical features. After up to 5 years of treatment (average observation period 37 months), the drug proved to be well tolerated and safe, without any serious hematologic or neurologic adverse event.

Despite the significant limits inherent the observational nature of the study and the limited numerical sample of our cohort, we are able to achieve some important conclusions confirming the potential benefit of long-term iron chelation.

First, DFP leads to reduction in brain iron deposits over time. Combining quantitative and qualitative MRI evaluations, we were able to observe a brain iron reduction in all our patients with SS.

Second, there may be a clinical correlation to the reduced brain iron in MRI and the stabilization in disease progression in at least one neurological domain (most commonly balance and dysarthria). It is also to underline that the best results have been achieved in patients with longer treatment periods and shorter delay between symptom onset and treatment initiation.

Table 3 MRI quantitative analysis (Mean T2/Max CSF)*

Subject	Pre-drug	Post-drug	Difference*
1	0.380	0.405 (1 year)	+ 0.025
2	0.395	0.497 (2 years)	+ 0.102
3	Not suitable	Not suitable	
4	0.191	0.389 (2 years)	+ 0.198

*A "positive" difference seems to indicate a decrease in total brain iron

Our results, combined with findings from previous studies [13], suggest that DFP may be clinically effective in SS. Even though iron abnormal deposition does not represent the initiating factor triggering neurodegeneration, it still remains one of the main steps of the pathological cascade and, hitherto, the more effectively targetable factor for therapeutic purposes since the introduction of DFP, able to specifically reduce the brain iron excess.

Long-term natural history studies in SS population are sparse. In 2007, Levy and Llinas [2] published the most extensive analysis of SS to date with a review of 270 case reports published. In this analysis, they reported that the natural history of SS is an invariably progressive neurological decline.

Our study is therefore significant because it represents a confirmation of the possibility to achieve a clinical benefit in a disease that previously could not be halted. Apart from DFP [13], there have been no successful treatment options that could stop the progression, much less improve outcomes. Only one case report described a patient who underwent surgical correction of the bleeding with subsequent improvement in neurological function, but long-term follow-up, beyond 15 months, was not yet available in that case [11].

Our findings confirm also what emerged in the work carried out on patients with NBIA regarding the safety of chronic treatment with DFP in diseases with intracerebral iron accumulation. There was no long-standing toxicity or development of agranulocytosis or decline in in this 5-year study. In previous studies, a 1–2% risk of agranulocytosis has been reported [13].

Moreover, our study suggests that the treatment efficacy enhances when it is started right after diagnosis, when symptoms are less severe and neurodegeneration probably less advanced.

In conclusion, the data from our work underline the long-term safety and tolerability of DFP as a chelator agent for intra- and extraneuronal iron accumulation. The enduring stabilization/slight improvement of symptoms observed in our patients over a prolonged observation period, together with the MRI data, suggests that DFP may be effective in the management of the—otherwise not treatable—neurological manifestations linked with iron accumulation in SS. However, these results need to be confirmed in a larger randomized study with a longer observation time.

Compliance with ethical standards

The trial was approved by the E.O. Ospedali Galliera Ethics Committee, and all participants gave written informed consent before entering the study (Clinicaltrials.gov identifier: NTC00907283).

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Fearnley JM, Stevens JM, Rudge P (1995) SS of the central nervous system. Brain 118:1051–1066
2. Levy M, Turtzo C, Llinas RH (2007) Superficial siderosis: a case report and review of the literature. Nat Clin Pract Neurol 3:54–58
3. Kumar N, Lane JI, Piepgras DG (2009) Superficial siderosis: sealing the defect. Neurology 72:671–673
4. Koeppen AH, Dentinger MP (1988) Brain hemosiderin and SS of the central nervous system. J Neuropathol Exp Neurol 47:249–270
5. Parnes SM, Weaver SA (1992) Superficial Siderosis of the central nervous system: a neglected cause of sensorineural hearing loss. Otolaryngol Head Neck Surg 107:69–77
6. Fredenburg AM, Sethi RK, Allen DD, Yokel RA (1996) The pharmacokinetics and blood-brain barrier permeation of the chelators 1, 2 dimethyl-, 1,2 diethyl-,and 1-[ethan-1'ol]-2-methyl-3-hydroxypyridin-4-one in the rat. Toxicology 108:191e9
7. Abbruzzese G, Cossu G, Balocco M, Marchese R, Murgia D, Melis M, Galanello R, Barella S, Matta G, Ruffinengo U, Bonuccelli U, Forni GL (2011) A pilot trial of deferiprone for neurodegeneration with brain iron accumulation. Haematologica 96:1708–1711
8. Cossu G, Abbruzzese G, Matta G, Murgia D, Melis M, Ricchi V, Galanello R, Barella S, Origa R, Balocco M, Pelosin E, Marchese R, Ruffinengo U, Forni GL (2014) 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. Parkinsonism Relat Disord 20:651–654
9. Pandolfo M, Arpa J, Delatycki MB, Le Quan Sang KH, Mariotti C, Munnich A, Sanz-Gallego I, Tai G, Tarnopolsky MA, Taroni F, Spino M, Tricta F (2014) Deferiprone in Friedreich ataxia: a 6-month randomized controlled trial. Ann Neurol 76:509–521
10. Cummins G, Crundwell G, Baguley D, Lennox G (2013) Treatment of superficial siderosis with iron chelation therapy. BMJ Case Rep 2013:bcr2013009916. https://doi.org/10.1136/bcr-2013-009916
11. Levy M, Llinas R (2012) Update on a patient with superficial siderosis on deferiprone. AJNR Am J Neuroradiol 33:E99–E100
12. Levy M, Llinas R (2012) Pilot safety trial of deferiprone in 10 subjects with superficial siderosis. Stroke 43:120–124
13. Kessler RA, Li X, Schwartz K, Huang H, Mealy MA, Levy M (2018) Two-year observational study of deferiprone in superficial siderosis. CNS Neurosci Ther 24:187–192