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Oral iron chelating therapy. A single center interim report on deferiprone (L1) in thalassemia

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ABSTRACT

Background and Objective. Deferiprone (L1) is a largely studied oral chelator in clinical setting, however, no definite conclusions concerning efficacy and toxicity still could be drawn. In an ongoing prospective trial with L1, we evaluated the efficacy and tolerance-toxicity in patients with thalassemia major previously treated by desferrioxamine (DFO); the specific aim of the study is to demonstrate that L1 could be an alternative to DFO in some patients with an acceptable toxicity.

Design and Methods. Sixty-nine patients over 13 years of age with poor compliance to DFO were considered for the study. The design included a liver biopsy before starting L1 in all patients in order to define liver siderosis either by histologic grading or by hepatic iron concentration (HIC); only patients with a minimum HIC of 4 mg/g dry weight entered the study. A repetition of the liver biopsy after one year of L1 was planned; further evaluations included serum ferritin, plasma iron, transferrin TIBC and iron urine excretion. L1 was given at 70 mg/kg/day in three divided doses. Toxicity was monitored either clinically or by controlling liver, kidney and marrow function by specific tests. Concerning clinical characteristics 52 patients showed hypogonadism (78%), 39 growth retardation (58%), 6 diabetes (9%), 4 cardiomyopathy (6%), 9 hypothyroidism (12%); 45 patients had chronic liver damage (65%).

Results. We focus this report on data collected in a group of 29 patients with a minimum follow-up of one year (14-33 months). The mean ferritin value was 3748 ng/mL (range: 200-10000) and 2550 ng/mL (range: 80-14500), before and while on L1 therapy, respectively (p=0.001); the mean sideruria changed from 17.25 mg/dL (range: 5.4-50) to 20.98 mg/dL (range: 10-40), on DFO and L1, respectively (p=0.078); the ratio between plasma iron (sideremia) and transferrin TIBC changed from 0.96 with DFO to 0.86 with L1 (0.014). A correlation with grade of liver siderosis and serum ferritin (p=0.069) and iron urine excretion (p=0.008) was recorded. The judgement of efficacy showed that L1 was effective (EF) in 9 patients, not assessable (UN) in 11 patients, not effective (NE) in 2 patients and with no advantages with respect to DFO in 7 patients. Liver biopsy was repeated in 20 patients showing a reduction of grade of liver siderosis and iron content in 7 patients. Clinical toxic effects of L1 were gastric intolerance (one patient), joint pain (three patients) and mild and temporary neutropenia (one patient).

Interpretation and Conclusions. This preliminary experience shows that L1 is effective in several patients with thalassemia with poor compliance to DFO and to improve iron burden and iron excretion with generally minor side effects. L1 could be an alternative to DFO in some patients, however the recognition of neutropenia warrants a careful evaluation of patients and efforts finalized to early recognition of those to be addressed with this new and still experimental therapy.

Key words: thalassemia, siderosis, desferrioxamine, oral iron chelation

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Desferrioxamine (DFO), as long term iron chelating therapy, has changed the quality of life and prolonged survival of patients with thalassemia;[1] more recently Olivieri *et al.*, emphasized the prediction of survival by the incidence of cardiac complications in relation to the accuracy of iron chelation by DFO.[2] However, many patients show a poor compliance to DFO in western countries due to the need of long term infusion; in addition, the high cost of DFO makes it unavailable for the vast majority of patients world-wide receiving long-term transfusional therapy. Therefore the development of an alternative, orally effective and less expensive iron chelator drug is needed.

Among potentially useful oral chelators only one of these, 1,2-dimethyl-3-hydroxypyridin-4-one (deferiprone or L1) has been demonstrated to be clinically effective, generally safe, and much less expensive than DFO, being to date the most promising for larger use in humans.[3,4] Nevertheless, in some cases, the long-term therapy with L1 has been associated with important complications such as severe, although reversible,

neutropenia[4] and less severe side effects such as nausea and artropathies in some patients. Despite these negative effects the use of L1 world wide is increasing, although definite conclusions on protocol designs and the choice of patients to be introduced to this chelating therapy are lacking and well-controlled prospective studies are needed for such conclusions. Being aware of difficulties in leading prospective randomized studies in patients with thalassemia, as recently emphasized,[5] we report the experience of a controlled non randomized study produced in a single institution with the aim to give an *interim* analysis for clinical usage for those who are beginning to treat patients with thalassemia by L1.

Materials and Methods

Patient selection

Patients over 13 years of age with thalassemia under chelating therapy with DFO were given the possibility to be treated by L1 if one of the following conditions were met: a) severe secondary siderosis despite the regular therapy with DFO; b) low compliance to DFO with less than 50% of expected intake of DFO associated to moderate or severe siderosis; c) well defined side effects to DFO and the impossibility to administer it regularly.

The siderosis was evaluated in all patients as already reported[6] giving a major relevance to the detection of iron content in the liver by liver biopsy and iron quantification. Only patients with iron liver content equal or exceeding 4.0 mg/g of liver dry weight were considered eligible. The compliance to DFO was assessed by the mean administration of DFO in the last year. Those with less than 180 days mean administration of therapy were considered not in compliance to DFO according to a previous report.[5] Local side effects included pain during DFO infusion, skin or subcutaneous indurations or infiltrations, bullas, aeritema, escaras. General side effects were fever, frequent infections, pruritus, skin rash, visus reduction and ipoacusia. Patients with a recurrence of these side effects were eligible for L1.

Sixty-nine patients (Table 1) among 120 patients who underwent liver biopsy and had a detection of iron content in the liver met the criteria for L1 therapy. Each patient received blood transfusions at two to four weeks interval in order to mantain the hemoglobin concentration over 10 g per deciliter with a mean packed red blood cells transfused of about 200 g per kg per year. All patients that entered the study with L1 had positive antibodies to HCV and 51 of them (73%) had elevation of ALT at least twice the normal value. Liver biopsies were performed as previously reported[5] by a Menghini's needle ensuring a tissue core of 2 cm in length when possible of which the more superficial half was sent to our pathology department for routine histological examination of liver and definition of iron load according to the method of Sheuer *et al.*,[7] the other half went to the laboratory for chemical quantification of iron with the method extensively reported in a previous work.[6] The weight of liver biopsies ranged from 0.49g to 6.81g (mean 3.15g) with a dry weight ranging from 7.8% to 37.3%. Forty-five patients (Table 1) showed liver damage with an inflammatory situation due to active chronic hepatitis (13 patients), persistent chronic hepatitis (14) or cirrhosis (18); other 24 patients showed aspecific alterations of the liver (14) or a normal picture (10) out of liver siderosis. Grade of liver siderosis before treatment with L1 was reported in Table 1; 11 patients had grade I, 16 grade II, 27 grade III and 15 grade IV.

An informed consent to be treated by an experimental therapy was requested to all patients. The protocol, approved by our local ethical committee, consisted of Deferiprone given orally at 70 mg/kg/day in three subdivided doses at empty stomach. *Apotek Inc.* provided the drug in vials containing 125 tablets of 500 mg.

The group of patients treated by L1 included only adolescents and adults with a mean age of 22 years (min. 13y, max. 30y); there were 35 females and 34 males all with low compliance to DFO. The main clinical data at the beginning of L1 therapy are summarized in Table 1. Fifty-two patients (78%) had primary or secondary hypogonadism, 39 patients (58%) had hypoevolutism or reduction of growth. Hypogonadism was defined as no occurrence of puberty (primary) or early disappearance of menstrual cycle in female (secondary) with a general reduction of development of secondary sexual characteristics and presence of infertility. Growth retardation resulted in a reduced epiphysial development and bone age.

Four patients had manifest cardiomyopathy, 6

Table 1. Main clinical and bioptic liver features of patients with thalassemia addressed to L1 herapy.

Total no. of patients	69
Sex (male/female)	34/35
Mean age (range)(yrs)	22 (13-30)
Hypogonadism	52 (78%)
Growth retardation	39 (58%)
Diabetics (insulin-dependent)	6 (9%)
Cardiomiopathy	4 (6%)
Hypothyroidism	9 (12%)
Hypoparathyroidism	4 (6%)
Liver damage	45 (65%)
active chronic hepatitis	13
persistent chronic hepatitis	14
cirrhosis	18
aspecific	14
normal	10
Liver siderosis	
I/II	11/16
III/IV	27/15

Table 2. Follow-up data of patients with thalassemia under chelating therapy with L1.

L1 therapy	69 pts
Under therapy	64
Off therapy	5
unrelated death (accident, suicide)	2
voluntary interruptions	2
gastric intolerance	1
Mean follow-up (range)	9.52 months (3-36)
More than one year follow-up	29 pts

patients had insulin-dependent type 1 diabetes, 9 patients had clinically-evident hypothyroidism and 4 had hypoparathyroidism.

Detection of efficacy

The body iron burden was assayed using chemical analysis of the liver obtained by percutaneous biopsy; the amount of iron was reported in mg/g dry weight of liver tissue, the method used for iron content was the same as previously reported in details.[6] Serum ferritin, plasma iron, transferrin TIBC (*total iron binding capacity*) and iron excretion by urine were detected monthly. Serum ferritin was measured in ng/mL, plasma iron in ug/dL, transferrin TIBC in ug/dL and urine iron excretion in mg/dL. The data reported in Tables 3 and 4 concerning the above parameters before the start of L1 or while on L1 represent the mean values recorded in the last three months before the beginning of the study and the three last evaluations while on study with L1. An adjunctive parameter of efficacy was also taken into consideration between the ratio of plasma iron and transferrin TIBC. This ratio was chosen as a parameter because there is less possibility for error in the evaluation of data considering that heavy siderosis implies a ratio between plasma iron and transferrin TIBC of 1 or more and it decreases when desaturated transferrin increases. The ratio was calculated by the sum of all mean values of the 29 patients with a minimum follow-up, while on L1, of one year (Table 3). The characterization of efficacy was done according to 4 definitions. The L1 was considered effective in reducing siderosis (EF) if at least 2 parameters such as ferritin, plasma iron and transferrin ratio, grade of liver siderosis, and liver iron content (LIC) were reduced of a minimum of one fourth in respect to the previous situation with DFO. In addition, a steady-state of other parameters and a constant urine iron elimination almost similar to that reported before L1 should be included. The L1 was considered not effective (NE) if at least 2 of the parameters worsened. The efficacy of L1 was considered unassessable (UN) if at least one or more parameters were controversial. Finally, L1 was considered as effective as DFO when all parameters remained almost unchanged (NC).

Table 3A. Details of 29 patients with thalassemia treated with L1 with follow-up exceeding one year. Data are referred to patients before treatment with L1.

Pts	*FU months*	*Ferritin ng/mL*	*Liver iron content LIC=mg/dL*	*Urine iron mg/dL*	*Grade liver siderosis histology*
Pre L1 therapy					
AGP	33	10,000	18	11	IV
AF	26	5,000	14.7	7	III
AG	14	5,200	12.1	12	III
BRS	30	5,100	16.5	13	IV
CE	30	1,200	14.4	11	II
CM	14	8,000	64.6	25.5	IV
CAP	16	6,600	21.1	30	IV
CG	16	7,000	13.0	20	IV
CM	30	1,800	10.6	6.4	III
CF	30	2,400	8	5.4	III
CC	29	4,800	24.8	34	IV
CF	20	4,500	22.6	50	IV
DA	20	200	13.1	12	III
DN	20	800	9.7	15	III
GM	20	3,500	16.4	9	III
FC	18	504	10.9	15	IV
MV	20	5,500	12.9	28	IV
MA	19	4,000	24.2	18	III
MM	29	2,700	13.2	11.7	III
MP	32	2,500	10.0	10	II
ML	19	2,500	5.4	16	I
NG	12	3,100	11.2	10	III
PR	14	1,000	10.3	27.9	III
PN	14	6,000	13.2	19.3	IV
PU	20	3,000	10.8	5	III-IV
QF	14	1,100	8.4	24.4	III
SMA	21	3,500	10.6	14.4	III
TM	21	9,500	18.9	28.5	IV
VMG	30	1,500	4.0	15	II

Statistical analysis

Statistical analysis was carried out with the non-parametric tests that are considered useful for abnormally distributed data due to a small patient sample by using the Mann-Whitney U-test; this was employed for comparing the mean values of non dichotomous discrete variables such as grade of liver siderosis versus serum ferritin and iron urine excretion. Pairs of data were analyzed by Wilcoxon's text taking into account mean values of serum ferritin and iron urine excretion pre-L1 and while on L1.

Detection of safety

Each side effect was observed by the patients and promptly referred to the Center particularly taking into consideration subjective symptoms such as fever, pain and swelling of the knees, anorexia, vomiting, headache, weakness, weight loss or weight gain. Objective evaluation consisted of a monthly physical examination and bi-weekly blood tests including

Table 3B. Details of 29 patients with thalassemia treated with L1 with follow-up exceeding one year. Data are referred to patients while on L1 therapy.

Pts	FU months	Ferritin ng/mL	Liver iron content LIC=mg/dlr	Urine iron mg/dL	Grade liver siderosis Histology	Tolerance	Efficacy
Post L1 therapy							
AGP	33	6,100	24	27	III	Good	EF
AF	26	6,000	9.9	14.2	III	Godd	EF
AG	14	1,400	6.3	30	II	Godd	EF
BRS	30	1,150	18	26	III	Good	EF
CE	30	270	6.6	16	II	RA+(no sint.)	UN
CM	14	4,700	100	40	IV	Good	NC
CAP	16	2,700	–	30	–	Good	UN
CG	16	2,700	11	30	III	Good	EF
CM	30	1,700	24	20.5	III-IV	Gonalgia	NC
CF	30	2,500	17.5	20	III	Gonalgia	NC
CC	29	1,700	18.4	20	III	Good	EF
CF	20	1,626	23.9	25	II	RA+(no sint.)	EF
DA	20	160	–	15	–	Good	UN
DN	20	80	–	20	–	Good	EF
GM	20	2,700	–	15	–	Good	UN
FC	18	505	–	26	–	Good	NC
MV	20	2,000	11.3	18.8	III	Mild-neutr.	UN
MA	19	2,000	–	30	–	Good	UN
MM	29	2,300	19.6	20	III	Good	UN
MP	32	2,200	22.7	15	III	Good	NE
ML	19	2,300	–	13	–	Good	NC
NG	12	1,500	6	15	III	Good	UN
PR	14	145	–	15	–	Gonalgia-RA+	UN
PN	14	4,800	26	10.5	I	RA+(no sint.)	NE
PU	20	2,500	15	10	IV	Good	UN
QF	14	827	22.1	19.7	III	Good	UN
SMA	21	1,200	–	21.8	–	Good	EF
TM	21	14,500	20	20	IV	Good	NC
VMG	30	1,700	5	15	II	Good	NC

Abbreviations: EF= effective; UN = unassessable; NE = not effective; NC = no change.

Table 4. Summary of results of oral chelating therapy in 29 patients with a follow-up exceeding 12 months. Biopsy data are referred to 20 patients who underwent second liver biopsy after 12 months of follow-up.

		Pre-L1	*Post-L1*	*p*
Follow-up		21.8 months (14-32)		
Sider./Trans.		0.96	0.86	0.014
Serum ferritin (ng/mL)		3,748 (200-10,000)	2,550 (80-14,500)	0.001
Liver iron content (mg/g)		16.09 (40-64.6)	20.99 (5-100)	ns
Sideruria (mg/dL)		17.25 (5.4-50)	20.98 (10-40)	0.044
Grade of liver siderosis: (on 20 patients)	I	1	1	
	II	2	4	
	III	8	12	
	IV	9	3	

WBC with differential count, platelets, hemoglobin, renal and liver function, coagulation tests in addition to the urine evaluation.

Results

Among sixty-nine patients entered in the evaluation, we considered those with a minimum follow-up of one year for this report (Table 2); there were 29 patients excluding two patients who died accidentally for causes unrelated to L1 therapy and 3 patients withdrawn from the evaluation because of major protocol violations and gastric intolerance. Table 3 details data concerning all 29 patients with a minimum follow-up of one year and maximum of 33 months (mean=21.75); data concerning serum ferritin, plasma iron and transferrin TIBC ratio, and iron urine excretion are reported for all patients before the start of L1 and at the follow-up, while data concerning biopsy of the liver with grade of liver siderosis and iron content of the liver are available in all patients at the beginning of therapy with L1 and in 20 patients at the first bioptical evaluation following almost one year of therapy with L1.

The single patient's tolerance reported in Table 3 shows that 22 patients had a good acceptability to the drug despite the number of tablets per day to be taken, 3 patients had Ra-test asymptomatic positivity, 3 patients had gonalgia with one Ra-test positive, and one mild and transient neutropenia. Table 3 also shows the judgment of efficacy to L1; 9 patients were considered to have definitely benefited by L1 (EF), 11 were almost not assessable (UN), 7 were considered to show no changes (NC), and 2 showed a worsened iron load (NE).

Table 4 shows the summary of data for the 29 patients before and while on L1 therapy concerning the mean ratio between the plasma iron (sideremia) and transferrin TIBC, mean serum ferritin, mean iron excretion by urine, iron content in the liver (for 20 patients after beginning of L1) and grade of liver siderosis. Serum ferritin was significantly reduced (p=0.001) from 3748 to 2550 ng/mL mean value; urine iron excretions changed in their mean values with a trend significance (p=0.078) and ratio between sideremia and serum transferrin with a significant positive decrease (p=0.014).

In addition, the analysis of data show that a positive trend was recorded between grade IV liver siderosis and serum ferritin reduction (p=0.069), and a significance was recorded between grade of liver siderosis and iron urine excretion (p=0.008). The only parameter which worsened as mean value was iron detection in the liver (LIC), available in 20 patients while on L1 (16.09 before and 20.99 while on L1); the details reported in Table 3 show that 7 patients had an improvement of LIC, 12 patients had a worsened situation and 1 remained almost unchanged.

Discussion

The adequate iron chelation together with the maintenance of hemoglobin level over 10 g × dL represent the main objectives in thalassemia major in order to improve survival.[7,8] The iron chelation is considered successful when the iron burden in the body is maintained under toxic level for heart, liver and endocrine glands and generally it occurs when chelation is given regularly and at an adequate dosage. Obviously, the availability of an efficacious compound for the chelation of iron given orally must represent an important advantage for patients who need a continuous iron chelation and show intolerance or eventually resistance to DFO. Furthermore, there are some patients with hematological diseases chronically transfused who are unable to receive DFO subcutaneously because of thrombocytopenia; in this particular subset of patients, an orally effective iron chelating compound is warranted.

L1 has been reported as effective in several reports[4,5,9-14] in reducing iron burden in patients with severe siderosis affected by thalassemia or other hematological malignancies; however, in the most recent final report on L1, Olivieri *et al*.[5] came to different conclusions than previously reported, in which L1 was definitely considered less effective than DFO in controlling iron burden in patients with thalassemia. It should be emphasized that the data reported[2] demonstrate that L1 exerts a major effect in patients with a higher iron burden and, in long-term therapy, L1 has been reported generally safe with few exceptions – consisting in reversible agranulocytosis.

Our data, although preliminary, confirm this general outlook (see Table 3) with a major urinary iron excretion in those patients with iron exceeding 15.0 mg/g of dry weight of the liver or serum ferritin over 4000 ng/mL. Instead in patients with the above parameters under these limits results are more controversial. In some cases, we were able to conclude that L1 is not more effective than DFO and in a number of patients definite conclusions couldn't be drawn. In addition, sporadic patients have shown data that definitely worsens with L1. One comment should be made about data recorded on HIC values showed many discrepancies and worsened in several patients; we believe that these data should be cautiously considered because in a short follow-up we cannot make definite conclusions, especially, due to the fact that, mainly in heavy siderosis, the iron in the tissue core of the liver is heterogeneously distributed.

Regarding a study with L1 treatment in patients with thalassemia, we were aware of a number of biases due to difficulties of leading heterogeneous patients and data drawing clear conclusions. The first bias was the difficulty of submitting a sufficient number of patients to a second liver biopsy as a monitor of HIC: most of them refused a second biopsy. A second bias is connected to the heterogeneity of iron burden in patients who already were under a chelating therapy by DFO, though with a poor compliance. This is the most powerful parameter for being treated by L1; many patients had discrepancies in recognized parameters, especially between ferritin level and HIC as also reported before.[6] These discrepancies could be explained by the heterogeneity of clinical data; our population of patients had a thalassemia major but some of them had a clinically intermedia form which generally exerts a greater accumulation of the iron in the liver due to major gastroenteric absorption than by transfusion iron load. A third bias was connected to the difficulty to compare ferritin level to other parameters being aware that ferritin could depend on inflammatory status of the liver and HCV activity. A further limit of this study is that we lack the evaluation of fecal iron excretion. However, despite these biases, our work warrants consideration, expecially when no clear conclusions in this field are available and our data, although in some aspects controversial, clearly show that some patients could benefit from L1.

This study was principally focused on preliminary results following L1 and tolerance at a follow-up exceeding one year of therapy. Considering the former aspect, we conclude that L1 can be a therapeutic alternative to DFO, even if a warning is necessary in order to make definite conclusions, and a longer follow-up may be necessary in order to conclude if L1 could be considered safe and effective in most patients.

Contributions and Acknowledgments

MP: conception and design, analysis and interpretation of data; AB, LG, MC and PG: involved in clinical assessment of the patients; SMA and GR: analysis of iron content in the liver; SAM, SV, DMS: analysis of grading of the iron content in the liver and definition of the liver damage; SF: statistical analysis; MR: provider of L1 and critical reviewer.

Disclosures

Conflict of interest: none.

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