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Abstract: 1161
December 8, 1997
Oral Session: Clinical Sickle Cell Disease and Thalassemia
(Room 15A, San Diego Convention Center)

Final results of the randomized trial of deferiprone and deferoxamine.

NF Olivieri, GM Brittenham

Toronto, Canada and Cleveland, OH

Treatment with DFO reduces morbidity and improves survival in iron-loaded patients. Results of non-randomized trials of L1 suggest that long-term therapy may not adequately control body iron in most patients. A prospective randomized trial comparing the effectiveness of L1 and DFO was conducted in Toronto and Montreal and prematurely terminated in Toronto by Apotex Inc. in 1996. In Toronto, hepatic iron concentration determined by biopsy or magnetic susceptometry (SQUID) was monitored up to May 1997, when L1 was discontinued in all patients because of safety concerns. The primary endpoint of effectiveness, defined prospectively in the trial protocol, was the change in hepatic iron concentration from that determined by SQUID ≤12 months prior to randomization, and that determined by SQUID or biopsy after 24 months of treatment on study. None of the 7 Montreal patients had completed 24 months on study by May 1997; results reported are those for patients randomized in Toronto only. Between study initiation in 11/93 and completion of enrollment in 9/95, 64 patients were randomized in Toronto; 13 withdrew before completion of 24 months [6 from DFO due to: interruption of DFO due to poor growth or hearing loss (3); request for IV DFO (1); parental abandonment (1); relocation to the Middle East (1)]; and 7 from L1 due to: L1-induced agranulocytosis (2); pre-therapy neutropenia (2); therapy associated with neutropenia (1); request for IV DFO (1); cardiac transplantation (1)]. By May 1997 13 of the remaining 51 patients had still not completed 24 months on study, while 38 were eligible for evaluation of the primary endpoint. Final hepatic iron concentration was obtained in 37/38 patients; because of obesity, final SQUID could not be obtained in 1 patient who refused biopsy. At baseline, mean hepatic iron did not differ significantly in the 18 DFO-treated patients (6.9 ± 0.9 milligrams iron per gram tissue, dry weight [mg/g]) and the 19 L1-treated patients (8.9 ± 1.2 mg/g; $p \leq 0.1$). After 33 ± 1.0 (range 24-43) months, hepatic iron of the DFO-treated patients had not changed (final mean hepatic iron: 7.9 ± 1.3 mg/g) even though, because of titration of dose against anticipated drug toxicity, the mean dose of DFO in this study was low (36.7 ± 2.8 mg/kg/night). By contrast, hepatic iron in L1-treated patients increased significantly (final mean hepatic iron: 13.7 ± 1.2 mg/g; $p \leq 0.01$). Compliance with L1, measured with computerized bottles (94.9 ± 1.1%), was significantly better than with DFO, measured using ambulatory pumps (71.6 ± 3.7%; $P < 0.005$); only 4 of 18 DFO-treated patients administered ≥80% of prescribed drug. After 24 months, tissue iron exceeded 15 mg/g in 7 L1-treated and in 2 DFO-treated patients, placing these patients at heightened risks of cardiac disease and early death *(NEJM 1994; 331: 567).* Optimal control of body iron was observed in all DFO-treated patients who administered >70% of prescribed drug. These data, from the only randomized trial of these agents, demonstrate that mean body iron burden increases after two years of L1 despite excellent compliance; tissue iron reaches concentrations associated with iron-induced complications in 95% patients, even those who begin therapy with relatively low initial body iron burdens. By contrast, less regular compliance with low doses of DFO appears to maintain mean body iron burden within optimal range.

Iron overload and hemochromatosis

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Deferiprone versus Deferoxamine in Patients with Thalassemia Major: A Randomized Clinical Trial

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ABSTRACT: Deferiprone has been suggested as an effective oral chelation therapy for thalassemia major. To assess its clinical efficacy, we compared deferiprone with deferoxamine in a large multicenter randomized clinical trial. One-hundred forty-four consecutive patients with thalassemia major and serum ferritin between 1500 and 3000 ng/ml were randomly assigned to deferiprone (75 mg/kg/day) ($n = 71$) or deferoxamine (50 mg/kg/day) ($n = 73$) for 1 year. The main measure of efficacy was the reduction of serum ferritin. Liver and heart iron contents were assessed by magnetic resonance. Liver iron content and fibrosis stage variations were assessed on liver biopsy by the Ishak score in all patients willing to undergo liver biopsy before and after treatment. The mean serum ferritin reduction was 222 ± 783 ng/ml in the deferiprone and 232 ± 619 ng/ml in the deferoxamine group ($P = 0.81$). No difference in the reduction of liver and heart iron content was found by magnetic resonance between the two groups. Thirty-six patients accepted to undergo repeat liver biopsy: 21 in the deferiprone and 15 in the deferoxamine group. Their mean reduction of liver iron content was 1022 ± 3511 $\mu g/g$ of dry liver and 350 ± 524, respectively ($P = 0.4$). No difference in variation of the Ishak fibrosis stage was observed between the two groups. Treatment was discontinued because of reversible side effects in 5 patients in the deferiprone group (3 hypertransamin/asemia and 2 leukocytopenia) and in none in the deferoxamine group. These findings suggest that deferiprone may be as effective as deferoxamine in the treatment of thalassemia major with few mild and reversible side effects.

Key Words: L1 therapy; oral chelation; randomized clinical trial; chelation therapy; L1 efficacy; thalassemia major management.

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INTRODUCTION

Prognosis of patients with thalassemia major has dramatically improved in the past two decades as a consequence of improvement in transfusional and chelation therapy (1, 2). Deferoxamine B mesylate (DF), is widely accepted as the standard chelation therapy (2). However it requires overnight subcutaneous infusion and is associated with serious side-effects (3–11). For these reasons, several oral iron chelators have been studied. Among these, deferiprone (1,2-dimethyl-3-hydroxypyrid-4-one, also called L1) appears to be promising. In the only randomized clinical trial so far reported, including 20 patients, L1 proved to have the same chelating effect as subcutaneous DF (12). However several other uncontrolled and small studies reported contrasting results which are difficult to interpret because of different patients selection and different length of follow-up (13–26). We therefore carried out a randomized clinical trial comparing L1 with subcutaneous DF.

METHODS

Patients

All the patients with thalassemia major consecutively observed at the participating centers between September 1994 and October 1997 were considered eligible for the trial if they had a serum ferritin concentration equal to or lower than 3000 ng/ml. Before the trial all patients were treated by deferoxamine B mesylate therapy at dosage of 50 mg/kg given subcutaneously during a 12-h period usually overnight for 5 days a week.

We decided to exclude patients with greater serum ferritin concentrations to minimize the inclusion of patients with a serious risk of multiple organ damage from iron overload. The diagnosis of thalassemia major was based on accepted clinical and molecular criteria (27, 28).

The exclusion criteria were (a) known intolerance to one of the trial treatments; (b) presence of rheumatoid factor; (c) serum antinuclear-autoantibody (ANA); (d) platelet count $<100{,}000/mm^3$ or leukocyte $<3000/mm^3$; (e) severe liver damage indicated by ascites; (f) clinical evidence of heart failure; (g) sepsis; and (h) α-interferon treatment (29). Eligibility and exclusion criteria were checked at each participating center in the outpatient or day-hospital section where the patients were also seen throughout the whole follow-up period.

Interventions

The trial treatments were given according to following schedule: deferiprone, 75 mg/kg divided in three daily doses administered as 500 mg pills every 8 h; deferoxamine B mesylate, 50 mg/kg given subcutaneously during a 12-h period, usually overnight for 5 days a week. Deferiprone was obtained by Inselspital (Berne, Switzerland), Lipomed (Basel, Switzerland), CIPLA Ltd. (India) and Apotex (Toronto, Canada). The purity of the drug was assessed in random samples throughout the study at the School of Life, Basic Medical and Health Sciences–King's College London—by Professor R. C. Hider Laboratory, and always exceeded 98%.

The planned duration of treatment was 1 year. It was established that at the end of the trial each patient had to continue chelation therapy by the conventional therapy (i.e., DF) until the study analysis was completed. We decided to assess the treatment efficacy over a 1-year period, considering it unlikely that a clinically significant iron overload would develop in this relatively short time in patients treated with the experimental treatment with this baseline serum ferritin levels, even if L1 was less effective than DF.

Compliance with the trial treatment was assessed by counting the pills in each returned bag of deferiprone and by assessing the total dose of deferoxamine B mesylate consumed each week. Compliance was also checked by interviewing the patient relatives.

Standard transfusional therapy was aimed at maintaining the hemoglobin blood concentration ≥ 9.5 g/dl.

Objectives

The study objective was to compare the two treatments in the reduction of iron overload or to prevent its increase.

Outcomes

The main measure of the treatment efficacy was the difference between the serum ferritin concentration before and after 1 year of treatment. Secondary efficacy measures were (a) variation of liver iron content (LIC) measured as μg/gram of dry weight in patients willing to undergo liver biopsy prior and after the treatment period; (b) variation of liver and heart iron content estimated by NMR performed by a 0.5-T superconducting unit (Vectra, General Eletric Medical Systems, Paris, France) using 0.24-cm^2 operator-defined regions of interest (ROIs) and expressed as average intensity signal ratio (ISR) (30–33). (NMR was performed at the Institute of Radiology, University of Palermo for all patients); (c) heart function as assessed by the following parameters recorded on heart ultrasonography: left ventricular ejection fraction (LVEF), left ventricular shortening fraction (LVSF) and the ratio of the right ventricle telediastolic to the telesystolic area (mm^3) (RVDSR); (d) variation in 24-h urinary iron excretion (UIE) measured during treatment.

A liver biopsy before and after the treatment was performed in all the patients who accepted it, according to a standard technique, to assess liver iron content and fibrosis. Biopsies were blindly examined under code by two independent observers experienced in liver histology, unaware of the type of treatment and of timing of biopsies. Liver inflammation and fibrosis were rated according to the Ishak scoring system (34). Interobserver agreement beyond chance for the fibrosis score was assessed by the weighted kappa statistic (35).

Liver iron content was assessed by atomic spectrophotometry on liver biopsy and expressed as amount of iron in μg/g dry liver weight. All patients were seen once or twice a month in the outpatient or day-hospital section of each participating center, according to the transfusional requirement. Clinical and biochemical assessment was repeated monthly, according to a prefixed data form.

Adverse Events

Any potential adverse event was recorded and the relationship with the trial treatment was carefully investigated. Variation in liver fibrosis was investigated in all patients accepting to undergo liver biopsy before and after the trial treatment.

If an increase of ferritin levels more than 1000 ng/ml, confirmed by two determinations apart with respect to the previous values was detected during the study period, the treatment was stopped and the alternative therapy was started.

Sample Size

The sample size estimate was based on the expected mean reduction in serum ferritin concentration at the end of 1 year of treatment. Based on previous experience at the coordinating center we knew that in patients with initial serum ferritin below 3000 ng/ml and treated with subcutaneous DF, the mean reduction in serum ferritin after one year of therapy was 250 ng/ml with a standard deviation of 65 ng/ml. We assumed that a difference higher than 30 ng/ml with respect to this expected ferritin reduction with DF, would be clinically significant. Therefore we calculated that to detect a 30 ng/ml difference (i.e., from 250 to 220), 70 patients should be included per group (two sided test; $\alpha = 0.05$; $\beta = 0.80$).

Randomization

The randomization was based on a computer generated random list in permuted blocks of 10. The *randomization sequence* was generated at the Biometrics Institute of the University of Milano. To ensure *allocation concealment,* treatment was assigned by telephone contact of each participating center with a physician (FP) of the coordinating center who kept the randomization sequence, but was not otherwise involved in the study. *Treatment assignment* was done when the inclusion and exclusion criteria per each consecutively observed patient were verified and treatment was started within the following 24 h.

Assessments of Outcome

Because of the modality of administration of deferoxamine B mesylate, a double blind design was considered unethical. However all the outcomes assessments (determination of serum fer-

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ritin concentration, urinary iron excretion, liver iron content and fibrosis on liver biopsy, liver and heart iron content estimated by MRI, heart function on ultrasound) were done under code by physicians blinded to the trial treatment. Also the statistical analysis was performed under code at the Biometrics Institute of the University of Milano, by a biostatistician (A.M.) blinded to the trial treatment.

Statistical Methods

Means are reported with standard deviation (SD); proportions and differences between proportions are reported with 95% confidence intervals (CI). The statistical analysis was based on the intention to treat principle. Continue scale values were compared between the two study groups by paired t test or two-sample t test with equal variances, as appropriate, by using a logarithmic transformation whenever this improved the approximation to normal distribution. Differences in proportions observed on contingency tables were assessed by χ^2 analysis. A multiple linear regression analysis by a step-wise backward procedure was planned to identify potential confounding factors affecting the mean serum ferritin reduction at the end of the treatment period. The following set of variables to be included in the multivariable analysis was defined a priori: sex, age, splenectomy, total number of blood units transfused in the last 12 months before randomization, initial serum ferritin concentration, 24-h urinary iron excretion before randomization, cirrhosis, HBsAg, anti-HCV, diabetes, left ventricular ejection fraction, endocrine dysfunctions, number of transfusions during the study period, and trial treatment. All statistical analyses were performed by STATA 6 (1999 STATA Corp.).

Ethics

The study protocol conformed to the ethical guidelines of Declaration of Helsinki (36) and was approved by the local ethics committee for human investigations. The patients gave their written informed consent to participate in the study.

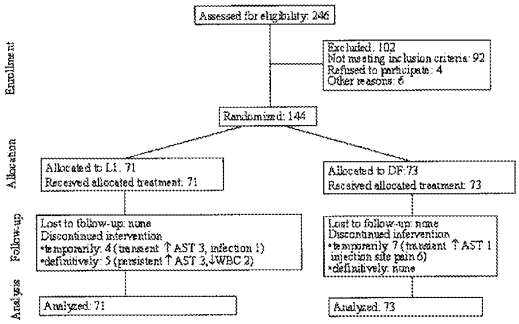

FIG. 1. Trial profile.

RESULTS

Participant Flow and Recruitment

From September 1994 to October 1997, 246 patients with thalassemia major were consecutively observed at the 15 participating centers. Among these patients 92 were not eligible because of serum ferritin concentration above 3000 ng/ml. Among the 154 eligible patients 3 were excluded because of ongoing α-interferon treatment, 3 because of rheumatoid factor positivity and 4 because of unwillingness to participate in the study. The remaining 144 patients were included: 71 were randomly assigned to L1 and 73 to DF. None of the patients was lost to follow-up (Fig. 1).

Eleven patients in the L1 group and 7 in the DF group with initial serum ferritin concentration over 3000 ng/ml were erroneously randomized. Individual data of these patients are shown in Table 5, and separate results are also reported for them.

Baseline Data

Clinically relevant patient characteristics at enrollment and corresponding values at the end of the one-year study period are shown in Tables 1–3.

Numbers Analyzed

All 71 patients randomized to L1 and 73 to DF were included in the analysis according to the "intention to treat" principle.

TABLE 1

Patients' Characteristics at Baseline

Characteristics	L1 group (n = 71)	L1 group with liver biopsy (n = 21)	DF group (n = 73)	DF group with liver biopsy (n = 15)
Age, years[a]	20 ± 5.3	19 ± 3.1	21 ± 4.2	20 ± 4
Sex (M/F)[a]	37/34	11/10	34/39	7/8
Total blood transfusions in the year before randomization, ml (mean ± SD)[a]	8,302 ± 541	8,000 ± 430	8,965 ± 278	8,700 ± 650
Total blood transfusions during the study, ml (mean ± SD)	10,142 ± 1071	8,985 ± 1694	9,181 ± 227	8,380 ± 1043
Mean serum ferritin in the year before randomization, ng/ml (mean ± SD)	2,159 ± 668	2,300 ± 590	2,074 ± 608	2,200 ± 650
Liver iron concentration, μg/gr dry liver (mean ± SD)	.....	3,363 ± 5,490[b]	.....	3,516 ± 2,974
HbsAg positive[a]	—	—	2	—
Anti-HCV positive[a]	59	16	65	11
Cirrhosis[a]	2	1	7	0
Splenectomy[a]	27	8	27	7
Diabetes[a]	1	—	2	—
Hypogonadism[a]	26	10	29	7
Hypothyroidism[a]	15	7	11	3
Hypoparathyroidism[a]	1	.....	4	1

Note. Data are numbers of patients unless otherwise stated.

[a] Variables included in the multiple linear regression analysis of confounding factors for the treatment effect.

[b] Liver iron concentration was measured in 20 patients of the L1 group because of insufficient material in one patient.

Treatment

Fifty-five patients per each trial group took the prescribed dose of the trial treatment during the whole study period; four patients in the L1 group and seven in the DF group took a reduced does because of low compliance. Twenty-four patients in the L1 group were not willing to switch to the conventional DF treatment at the end of the study period. After the recent report of a study suggesting that L1 may increase the risk of liver fibrosis (23), the patients who were still willing to continue L1 treatment were asked to undergo a second liver biopsy before continuing treatment.

Long-term variation of liver iron content and fibrosis of all these patients is reported (Tables 3 and 4; Figs. 2 and 3).

Adverse Events

In the L1 group, 24 patients developed side effects requiring temporary dose reduction in 3 (nausea) and temporary treatment withdrawal in 4 (transient hypertransaminasemia 3, infection 1). Five patients were definitively withdrawn from treatment because of recurrence of hypertransaminasemia (>2 times the pretreatment values) (n = 3, anti-HCV positive 1) or leukocytopenia (n = 2) even at reduced doses of the study drug. Mild hypertransaminasemia, spontaneously recovering developed in 10 other patients and mild joint pain in two. Overall, 14 of the 16 patients who developed hypertransaminasemia, were anti-HCV positive. Adverse events occurred in 11 DF treated patients: temporary dose reduction was needed in 6 patients because of pain and erythema at the injection site and in one because of transient hypertransaminasemia. Two patients developed infections (*Yersinia enterocolitica*) and two ototoxicity, requiring temporary treatment withdrawal. All of these patients continued on DF after temporary dosage reduction or temporary treatment withdrawal.

One patient per group was withdrawn from the trial treatment because of an increase of serum ferritin of more than 1000 ng/ml during the first 6

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TABLE 2

Relevant Blood and Biochemistry Parameters at Baseline and at the End of Treatment in the 144 Patients Included in the Study

	L1 group (n = 71)		DF group (n = 73)	
Parameter	Baseline	After treatment	Baseline	After treatment
Hemoglobin (g/dl)	10.3 ± 1.2	10.0 ± 0.9*	10.2 ± 1.4	10.0 ± 1.0
Leucocytes ($\times 10^9$/L)	9.4 ± 4.8	11.0 ± 7.9*	8.9 ± 5.8	9.1 ± 7.4
Platelets ($\times 10^9$/L)	369 ± 170	396 ± 184	344 ± 135	358 ± 147
Glucose (mg/dl)	98 ± 16	95 ± 17	97 ± 36	97 ± 18
Urea (mg/dl)	31 ± 10	30 ± 11	31 ± 10	32 ± 9
Creatinine (mg/dl)	0.7 ± 0.1	0.7 ± 0.2	0.7 ± 0.2	0.6 ± 0.2
Uric acid (mg/dl)	4.1 ± 1.2	4.2 ± 1.3	4.1 ± 1.3	4.3 ± 1.1
AST (U/L)	37 ± 24	55 ± 112	33 ± 23	34 ± 24
Anti-HCV positive	37 ± 25	59 ± 122	35 ± 24	36 ± 24
Anti-HCV negative	30 ± 17	30 ± 18	22 ± 12	22 ± 5
ALT (U/L)	58 ± 61	80 ± 125	50 ± 47	48 ± 46
Anti-HCV positive	61 ± 60	86 ± 135	53 ± 48	51 ± 47
Anti-HCV negative	29 ± 27	41 ± 38	26 ± 31	24 ± 12
γGT (U/L)	21 ± 14	35 ± 31**	21 ± 16	25 ± 24
Anti-HCV positive	23 ± 17	38 ± 33	22 ± 16	25 ± 25
Anti-HCV negative	12 ± 7	18 ± 9	12 ± 4	12 ± 5
Bilirubin (mg/dl)	1.4 ± 0.8	1.2 ± 0.6	1.4 ± 0.6	1.5 ± 0.7
Prothrombin activity (%)	84 ± 14	91 ± 11**	81 ± 13	85 ± 12
Albumin (g/dl)	4.5 ± 0.5	4.5 ± 0.9	4.5 ± 0.5	4.5 ± 0.9
γ-Globulins (g/dl)	2.3 ± 1.0	2.2 ± 0.9	2.4 ± 1.1	2.3 ± 1.1
Iron (μg/dl)	214 ± 49	216 ± 64	207 ± 49	201 ± 48
Transferrin (mg/dl)	215 ± 70	223 ± 76	215 ± 87	213 ± 91

Note. Data are means ± standard deviations. No significant differences were found at the end of treatment compared with baseline (paired t test) unless otherwise specified.

* $P < 0.05$ compared with baseline (paired t test).

** $P < 0.01$ compared with baseline (paired t test).

months of trial treatment. Four patients in the L1 group and seven in the DF group took a reduced dose because of low compliance.

Outcomes

Mean *serum ferritin* concentration before and after one year of treatment are reported in Table 3 and Figs. 4–7. The mean reduction in serum ferritin concentration was 222 ± 783 ng/ml in the L1 group and 232 ± 619 ng/ml in the DF group (P = 0.81) (Table 3). Corresponding results in patients with baseline serum ferritin equal or lower than 3000 ng/ml (n = 126) and above this value (n = 18) are reported in Tables 4 and 5, respectively.

Secondary Measures of Treatment Efficacy

NMR assessment of liver and heart iron content are reported in Table 3. A statistically significant increase in ISR was found after both treatments for all the NMR measurements, suggesting that a significant reduction in the iron content in the heart and in the liver was associated with the two trial treatments (Tables 3 and 4). This increase was not statistically significant for the liver in the L1 group (Tables 3 and 4) although the change in liver ISR after treatment was not significantly different between the two study groups (Tables 3 and 4).

Assessment of heart function by ultrasound did not show appreciable variation with either treatment after the study period (Table 3). The values of other clinically relevant parameters at the end of treatment are reported in Table 2. It is important to note that a slight but not statistically significant increase of transaminases was found after L1 treatment greater in anti-HCV positive patients; γGT significantly increased in

TABLE 3

Summary of Treatment Efficacy Assessment

Measures of treatment efficacy	L1 group (n = 71)			DF group (n = 73)		
	Baseline	End of treatment	Difference[a]	Baseline	End of treatment	Difference[a]
Serum ferritin (ng/ml)	2283 ± 754[g]	2061 ± 853*	222 ± 783	2019 ± 678	1787 ± 893*	232 ± 619
Liver iron concentration (μg/g/dry weight)[b]	3363 ± 5490	2341 ± 2197	1022 ± 3511	3516 ± 2974	3166 ± 2519	350 ± 524
Anti-HCV positive	3651 ± 5928	2506 ± 2321	1145 ± 3812	3483 ± 3049	3184 ± 2604	299 ± 487
Anti-HCV negative[c]	1731 ± 708	1353 ± 626	378 ± 192	3718 ± 3560	3046 ± 2734	672 ± 825
Urinary iron excretion (mg/24 h)	11.4 ± 8.5[g]	15.8 ± 10.9*	−4.4 ± 13.2	15.7 ± 12.8	19.9 ± 13.6**	−4.2 ± 12.5
Liver NMR[d]	0.83 ± 0.32	0.89 ± 0.26	−0.06 ± 0.38	0.85 ± 0.36	0.98 ± 0.35**	−0.13 ± 0.28
Heart septum NMR[d]	1.06 ± 0.20	1.18 ± 0.30*	−0.12 ± 0.32	0.98 ± 0.26	1.12 ± 0.29**	−0.14 ± 0.30
Left ventricular NMR[d]	1.02 ± 0.26	1.23 ± 0.46**	−0.21 ± 0.46	0.99 ± 0.27	1.12 ± 0.25*	−0.13 ± 0.31
Right ventricular NMR[d]	0.99 ± 0.24	1.22 ± 0.50**	−0.23 ± 0.50	0.97 ± 0.32	1.16 ± 0.32*	−0.19 ± 0.48
Left ventricular EF (%)[e]	63 ± 6[g]	63 ± 6	0 ± 8	62 ± 7	61 ± 7	1 ± 6
Left ventricular SF (%)[e]	41 ± 11	40 ± 8	1 ± 10	40 ± 12	38 ± 8	2 ± 9
Right ventricular area ratio[f]	1.9 ± 0.28	2.04 ± 0.32	−0.14 ± 0.42	1.9 ± 0.28	2.0 ± 0.18	0.1 ± 0.28

Note. Data are means ± standard deviations.

[a] Values at randomization minus values at the end of treatment. Differences were not statistically different between the two study groups (two-sample t test with equal variances).

[b] Liver iron concentration was measured in 20 and 15 patients in L1 and DF treatment groups.

[c] All patients anti-HCV negative had baseline ferritin levels lower or equal to 3000 ng/ml.

[d] NMR, nuclear magnetic resonance. Values are expressed as intensity signal ratios.

[e] EF, ejection fraction on ultrasonography.

[f] Teledyastolic/telesystolic area on ultrasonography.

[g] Variables included in the multiple linear regression analysis of confounding factors for the treatment effect.

* $P < 0.05$ compared with baseline (paired t test).

** $P < 0.01$ compared with baseline (paired t test).

anti-HCV positive patients (Table 2). Comparable results were observed in the 126 patients with baseline serum ferritin equal or lower than 3000 ng/ml.

Analysis of Confounding Factors

The multiple regression analysis performed to assess whether potential confounding factors (variables included are reported in the methods and corresponding values in Tables 1–3) might have affected the study results, confirmed that the type of the trial treatment as well as the baseline value of serum ferritin concentration, did not have any independent association with the size of serum ferritin reduction at the end of the study. The only two variables independently associated with a higher serum ferritin reduction were female sex ($P = 0.036$) and the number of blood units transfused in the year before randomization ($P = 0.033$).

Liver Iron Content (LIC)

Altogether 36 patients gave consent to undergo liver biopsy before and after treatment, 21 in the L1 group and 15 in the DF group (Table 1). In the L1 group the difference of liver iron content (LIC) between the two biopsies was assessed in 20 of them because one biopsy in one patient in the L1 group provided insufficient material. The mean follow-up until the second liver biopsy was 30 ± 2.4 months for L1 and 34 ± 6.7 for DF group, respectively. The distribution values of LIC before and after treatment is shown on Fig. 2. All the patients were still continuing the trial treatment at the time of the second biopsy. The mean values of LIC before and after treatment are reported in Table 3. The mean difference in liver iron content from before to after treatment was 1022 ± 3511 (median 317; range 1590 to 15570) in the

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TABLE 4

Summary of Treatment Efficacy Assessment in 126 Patients with Baseline Serum Ferritin Lower or Equal to 3000 ng/ml

Measures of treatment efficacy	L1 group (n = 60)			DF group (n = 66)		
	Baseline	End of treatment	Difference[a]	Baseline	End of treatment	Difference[a]
Serum ferritin (ng/ml)	2036 ± 463	1894 ± 760	142 ± 750	1877 ± 533	1678 ± 800**	198 ± 561
Liver iron concentration (μg/g/dry weight)[b]	3290 ± 5706	2191 ± 2229	1099 ± 3697	3500 ± 3232	3263 ± 2826	237 ± 506
Anti-HCV positive	3602 ± 6232	2358 ± 2408	1244 ± 4057	3457 ± 3369	3307 ± 2987	150 ± 433
Anti-HCV negative	1731 ± 708	1353 ± 626	378 ± 192	3718 ± 3560	3046 ± 2734	672 ± 825
Urinary iron excretion (mg/24 h)	11.6 ± 7.7	16.0 ± 11.3*	−4.5 ± 12.7	15.5 ± 13.1	19.8 ± 14.1*	−4.3 ± 12.8
Liver NMR[c]	0.83 ± 0.21	0.90 ± 0.26	−0.07 ± 0.38	0.87 ± 0.34	1.02 ± 0.33**	−0.15 ± 0.27
Heart septum NMR[c]	1.08 ± 0.19	1.19 ± 0.31*	−0.11 ± 0.33	0.96 ± 0.26	1.09 ± 0.28**	−0.13 ± 0.31
Left ventricular NMR[c]	1.02 ± 0.23	1.23 ± 0.40*	−0.21 ± 0.47	0.97 ± 0.27	1.07 ± 0.18	−0.10 ± 0.30
Right ventricular NMR[c]	0.99 ± 0.22	1.20 ± 0.50*	−0.21 ± 0.48	0.93 ± 0.30	1.13 ± 0.31*	−20 ± 49
Left ventricular EF (%)[d]	63 ± 7	62 ± 7	1 ± 8	63 ± 7	62 ± 7	1 ± 5
Left ventricular SF (%)[d]	42 ± 12	41 ± 8	1 ± 11	40 ± 12	38 ± 8	2 ± 8
Right ventricular area ratio[e]	1.9 ± 0.29	2.1 ± 0.29	−0.2 ± 0.39	1.9 ± 0.28	2 ± 0.26	0.1 ± 0.28

Note. Data are means ± standard deviations.

[a] Values at randomization minus values at the end of treatment. Differences were not statistically different between the two study groups (two-sample t test with equal variances).

[b] Liver iron concentration was measured in 20 and 15 patients in L1 and DF treatment groups.

[c] NMR, nuclear magnetic resonance. Values are expressed as intensity signal ratios.

[d] EF, ejection fraction on ultrasonography.

[e] Teledyastolic/telesystolic area on ultrasonography.

* $P < 0.05$ compared with baseline (paired t test).

** $P < 0.01$ compared with baseline (paired t test).

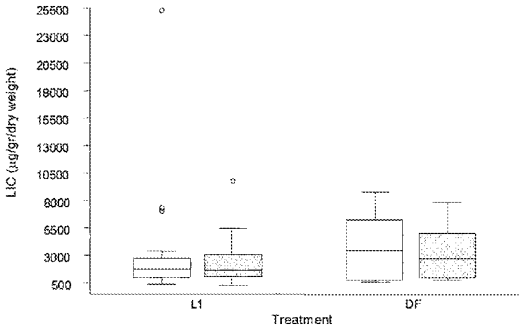

FIG. 2. Liver iron content (LIC) before (□) and after (▨) treatment. The mean follow-up until the second liver biopsy was 30 ± 2.4 months for L1 and 34 ± 6.7 for DF group, respectively. The lines emerging from the box indicate the upper and lower values. The upper values is defined as the largest data point greater than or equal to $x_{[75]} + 1.5x$ interquartile range; the lower value is defined as the smallest data point greater than or equal to $x_{[25]} - 1.5x$ interquartile range. Observed circles more extreme than the upper and lower values, if any, are referred to as *outside values* and are individually plotted.

L1 group and 350 ± 524 (median 272; range 405 to 1256) in the DF group ($P = 0.44$; $t = 0.77$) (Table 3). Relevant values according to the HCV status are reported in Table 3.

Liver Fibrosis

Liver biopsies from the 21 in the L1 (16 anti-HCV positive) (Table 1) and 15 in the DF group (11 anti-HCV positive) (Table 1) who accepted to undergo repeat biopsy, were blindly assessed under code for the degree of liver fibrosis by two independent observers. The interobserver agreement beyond chance as assessed by the k-weighted statistic was 0.59 ($P = 0.001$).

The mean of fibrosis scores before treatment were 2.1 ± 1.3 (median 2, range 1.5–2.7) in the L1 group and 2.2 ± 1.3 (median 2, range 1.5–3.05) in the DF group ($P = 0.77$). The corresponding values after treatment were not different from those before ($P = 0.84$; $t = -0.20$): 2.1 ± 1.5 (median 2, range 1.4–2.8) in the L1 group and 2.2 ± 1.2 (median 2, range 1.5–2.9) in the DF

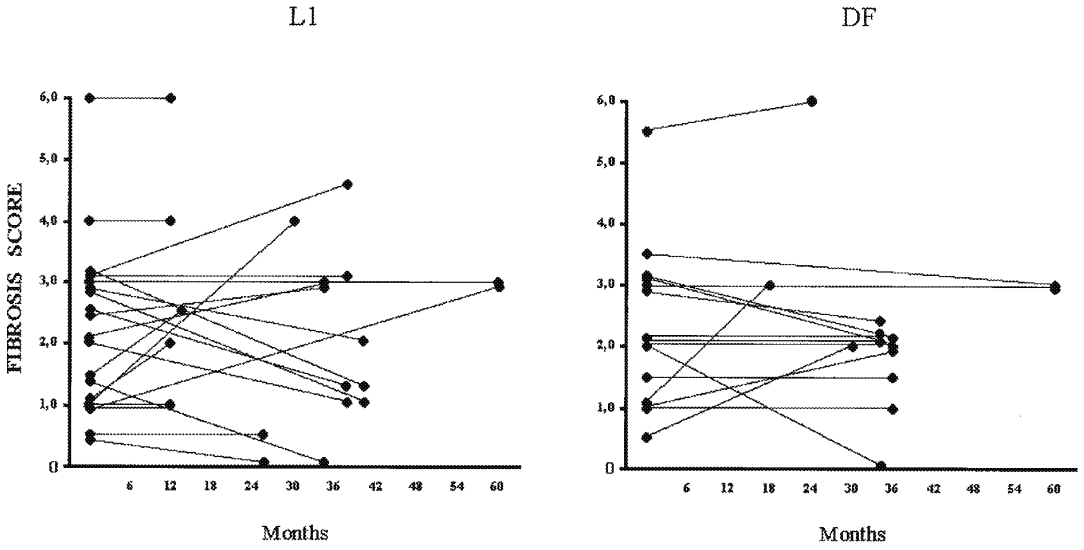

FIG. 3. Baseline and follow-up values of liver fibrosis score, represented as the mean value of the two independent observations performed by two independent observers unaware of the type of treatment and of timing of biopsies, in the 21 L1 and 15 DF patients who underwent repeat liver biopsy after treatment.

group (Fig. 3). Fibrosis score increased in 7 out of 21 patients in the L1 group and in 4 of 15 patients in DF group (Fig. 3). Among these patients 6 were anti-HCV positive in the L1 group and 4 in the DF group, respectively. Their mean initial vs final LIC values were 2360 ± 2313 (median 2084; range 506 to 7290) vs 2095 ± 1746 (median 2000; range 262 to 4800) in the L1 and 2270 ± 3173 (median 709; range 632 to 7030) vs 2318 ± 2737 (median 1031; range 790 to 6419) in the DF group. One in the L1 and 1 in the DF group, respectively discontinued treatment because of side effects.

DISCUSSION

Interpretation and overall evidence. This is the first large randomized clinical trial comparing L1

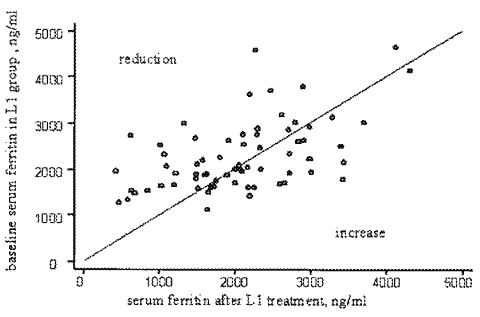

FIG. 4. Baseline and end of treatment values of serum ferritin in the 71 patients in L1 group. The diagonal line denotes equivalence values. Values above the equivalence line indicate reduction and those below the line indicate increase of ferritin after treatment.

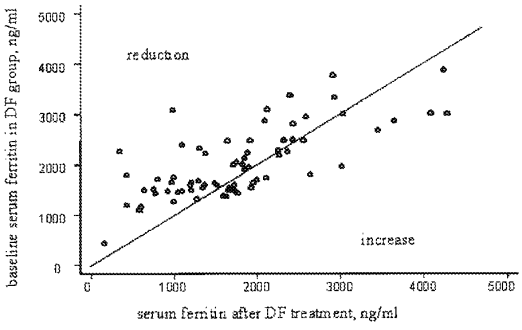

FIG. 5. Baseline and end of treatment values of serum ferritin in the 73 patients in DF group. The diagonal line denotes equivalence values. Values above the equivalence line indicate reduction and those below the line indicate increase of ferritin after treatment.

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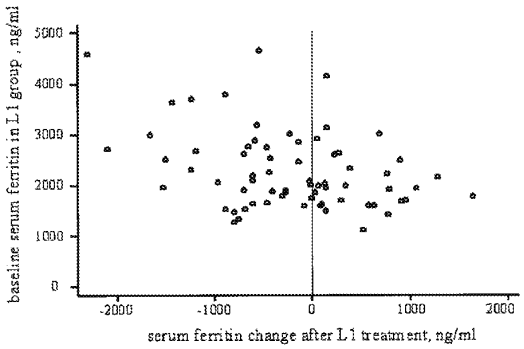

FIG. 6. Serum ferritin change from baseline to end of treatment according to baseline values in the 71 patients in L1 group. The vertical line indicates no change.

and DF for iron chelation in β-thalassemia. The results show that the two treatments cause a similar reduction in serum ferritin over one year, in patients with relatively low serum ferritin before treatment (Table 3, Figs. 4–7).

The study showed also several other indicators of a similar chelating effect of the two trial treatments. The most important is the mean reduction in the liver iron content. Although only 36/144 patients gave consent to undergo liver biopsy before and after treatment, the clinical characteristics of these 36 patients were comparable to the whole trial population and within the two treatment subgroups. The presence of not high LIC levels in both treated groups (Tables 1, 3, and 4) could be due to the reason that the selected subjects having relatively low serum ferritin levels, according to the main inclusion criteria, are representative of a well-chelated patients group in which beneficial effects of subcutaneous deferoxamine on iron loading within the liver has been shown (37, 38).

It is worth to note that although the liver iron overload was largely below the value previously suggested as a threshold for predicting a beneficial effect of L1 (14), the observed reduction of liver iron content might be clinically remarkable over a longer period of treatment. The comparability of the reduction of liver iron content achieved with the two treatments was also confirmed by the comparable increase of liver ISR assessed by NMR in the two treatment groups (Table 3). We previously showed a correlation in thalassemia major patients between liver ISR, assessed by the same NRM equipment used in this study, and Liver Iron Concentration (30).

The comparable increase of heart ISR on NMR (in the whole heart as well as in the left and in the right ventricles separately) as well as the lack of significant variations of the heart function we found in the two trial treatment groups, also adds to the evidence that the two treatments have similar effects on the overall iron overload.

Adverse events were more frequent with L1 (24/71 patients vs 11/73 patients), although the difference was almost entirely due to a moderate hypertransaminasemia which spontaneously subsided in ten patients. The recurrence of hypertransaminasemia when restarting the treatment caused a temporary treatment withdrawal in three and a definitive withdrawal in other three. Among this group of patients with hypertransaminasemia 14/16 (87%) were Anti-HCV positive. The other adverse events were few and mild, requiring a reduction of the drug dose only in 3 patients experiencing nausea. A marked leukopenia caused a definitive treatment withdrawal only in two other patients. In these two patient pre-treatment leukocyte count was achieved after stopping treatment. Therefore only in 5 of 24 patients experiencing adverse events with L1, treatment withdrawal was needed. However, all of the adverse events were reversible and not otherwise

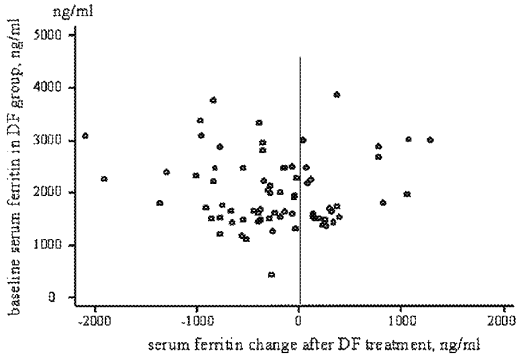

FIG. 7. Serum ferritin change from baseline to end of treatment according to baseline values in the 73 patients in DF group. The vertical line indicates no change.

TABLE 5

Individual Serum Ferritin Concentration at Baseline and at the End of the Treatment for 18 Patients with Baseline Values >3000 ng/ml

L1 group				DF group			
Patient ID	Baseline	End of treatment	Difference	Patient ID	Baseline	End of treatment	Difference
3	3630	2190	−1440	30	3760	2920	−840
4	3700	2470	−1230	57	3010	4090	1080
70	3010	3700	690	62	3330	2940	−390
103	4650	4110	−540	64	3090	2130	−960
104	4140	4300	160	82	3370	2400	−970
105	3180	2620	−560	117	3080	990	−2090
106	3790	2900	−890	126	3870	4250	380
115	3010	2790	−220				
120	3090	2060	−1030				
124	3130	3290	160				
142	4570	2270	−2300				
Total (n = 11)[a]	3627 ± 610	2973 ± 777*	654 ± 848**	Total (n = 7)[a]	3358 ± 340	2817 ± 1131	541 ± 1028

Note. Data are ng/ml. Difference is "end of treatment" value minus baseline value.
[a] Mean ± SD.
* $P < 0.05$ compared with baseline (paired t test).
** $P = 0.81$ compared with DF group (two-sample t test with equal variances).

clinically significant. Side effects with DF were observed in 11/73 patients and the most frequent was pain and erythema at the injection site which required a reduction of the drug dose in 6 patients.

We did not find any appreciable difference in liver fibrosis with the two treatments, in the patients who gave consent for a repeat liver biopsy. Fibrosis was blindly rated by two independent observers; they rated the fibrosis according to the same score (34) used in the Olivieri's study (23) and their agreement beyond chance was satisfactory (k-weighted = 0.59; $P < 0.0001$) (Fig. 3).

There are several possible explanations for the different findings on the progression of liver fibrosis in our study compared with that by Olivieri and colleagues (23). The mean follow-up was 55 months in the Olivieri's study and 30 months in the L1 treated patients in the present one; the initial serum ferritin concentration and liver iron content were distinctly lower in the present study; the two studies assessed a relatively low number of patients and the differences in the results may be due to chance. There are, however several methodological differences between the two studies, that have to be considered. The present study is prospective, the treatment was assigned by randomization, the control group was a parallel one, the interobserver agreement was assessed according to standard methodology and was satisfactory. All these methodological characteristics, were not met by the Olivieri's study, therefore making the comparability of the two studies uncertain. Our results agree with previous studies, reported by ourselves and other authors, giving liver biopsy data (either single or repeated) in patients receiving deferiprone (22, 39–42). Moreover, Cohen *et al.* (43) during a safety prospective multicenter study suggested that, although alanine transaminase (ALT) levels rose during therapy, the increase of ALT levels were generally transient and occurred more commonly in patients with virus C hepatitis. Thus, although our results concerning the risk of progression of fibrosis may not be considered conclusive, they at least suggest that whether L1 treatment is associated to such a risk remains still unsettled and that further well designed and well conducted studies to assess this specific point should be performed especially to assess if other factors as HCV or liver iron concentration could be involved.

Interpretation

This study shows that over a relatively short time period in patients with relatively low initial serum ferritin concentration, deferiprone has an

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iron chelating effect not significantly different from deferoxamine. Under the conditions of this study, deferiprone proved to be satisfactorily safe and the previously reported risk of progression of liver fibrosis with this drug was not confirmed.

Generalizability

According to the eligibility and exclusion criteria used in this study and the large ratio of recruited to excluded patients, it may be expected that the observed treatment effect may be reproduced in patients with thalassemia major and serum ferritin concentration below 3000 ng/ml over a 1-year treatment period. The results in the subgroup of patients with baseline serum ferritin above 3000 ng/ml suggest that deferiprone might be beneficial also in patients with higher values of ferritin. However this should be confirmed in future RCTs.

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Iron Chelation with Oral Deferiprone in Patients with Thalassemia

To the Editor: Olivieri et al. (Aug. 13 issue)[1] retrospectively evaluated liver-biopsy specimens from patients with thalassemia who were treated with deferiprone and concluded that progression of fibrosis in 5 of 14 patients was due to the drug. The authors minimized the potential role of known factors that could, on their own, explain the progression of fibrosis in the five patients and the fact that many had received inadequate chelation therapy before they started taking deferiprone. Fibrosis and even cirrhosis are prominent in patients with thalassemia, as illustrated by the fact that 3 of 18 patients had cirrhosis before treatment with deferiprone was begun. Most important, four of the five patients with progression had antibodies to hepatitis C virus (HCV), one of the major causes of hepatic fibrosis in patients with thalassemia. Moreover, the authors did not acknowledge studies that reported no deferiprone-induced progression of fibrosis.[2-4]

The slides of the biopsy specimens in the study by Olivieri et al. were reviewed by an independent histopathologist at the request of Apotex, the manufacturer of deferiprone and a sponsor of the study. This assessment revealed that most of the specimens were inadequate to allow firm conclusions to be drawn. However, if one disregarded the quality of the material, and assessed all the slides, one found an overall decline in fibrosis, not a progression.[4] Olivieri et al. received a copy of this review in 1997.

In a previous report on the same patients, Olivieri et al. stated that the patients were "unable or unwilling to use deferoxamine."[5] Under these circumstances, an increased iron load would have been inevitable. However, during treatment with deferiprone, only 4 of 18 patients appeared to have an increase in iron, whereas the levels were unchanged in 5 and declined substantially in 9, demonstrating that the drug was effective in removing iron even during continued transfusions.

Cirrhosis did not develop in any of the patients, none died, and none had a worsening of cardiac function.[1] In the absence of chelation therapy, there would have been a greatly increased iron burden, far worse progression of fibrosis, and probably some deaths. To prevent what appears to be a speculative risk of fibrosis, Olivieri et al. stopped deferiprone therapy in patients who "were unable or unwilling to use deferoxamine,"[5] thus exposing some of these patients to the life-threatening risks of iron overload.

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To the Editor: Olivieri et al. report that cirrhosis did not develop in any patient during treatment with deferiprone, according to the scoring system for fibrosis used by Ishak et al.[1]

In the accompanying editorial, Kowdley and Kaplan[2] note that the methods used by Olivieri et al. are flawed, in part because they accepted liver-biopsy specimens with as few as two portal tracts. The reliability of the scoring system of Ishak et al. is contingent on the presence of a sufficient

number of portal tracts; the acceptance of specimens with only two portal tracts renders the method virtually unusable.

The paucity of portal tracts in the specimens may explain the apparent absence of fibrosis (score, 0) in the pretreatment biopsy specimen in three of five patients who were reported as having evidence of progression of fibrosis. The absence of fibrosis would be highly unlikely in patients who were inadequately treated with a chelating agent, as is suggested by the high concentrations of serum ferritin and hepatic iron recorded before deferiprone therapy was initiated.

In April 1997, after the publication of the initial report by Olivieri et al.,[3] Apotex, the firm that manufactures deferiprone, asked me to review the entire series of biopsy specimens from these patients; I did so, with the permission of Toronto Hospital. The slides were coded and randomly arranged by Dr. Cameron, a coauthor of the study. After reviewing the slides in a blinded fashion, I provided Toronto Hospital and Apotex with a report. My review led to results and conclusions that differed substantially from those of Olivieri et al. In their paper, Olivieri et al. chose not to reveal that this review had taken place and that the results disagreed with theirs.

The limitations of the study, particularly those related to the size of the histologic samples, should have caused the authors to urge caution in the interpretation of their results, as opposed to expressing their conclusions so strongly.

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Editor's note: Dr. Callea is a paid consultant for Apotex.

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To the Editor: Preliminary assessment of deferiprone (the only oral iron-chelating agent that has been studied extensively) in children with β-thalassemia suggested that it might prevent the potentially fatal effects of the accumulation of iron due to blood transfusions. In longer-term studies,[1] however, hepatic iron concentrations were poorly controlled in many patients. In one series, nearly 60 percent of estimations of hepatic iron concentration obtained after extended treatment with deferiprone exceeded the safety threshold, above which there is an increased risk of cardiac disease and early death, established in studies of intravenous deferoxamine.[2] These observations and the new data of Olivieri et al. indicate that deferiprone does not consistently reduce body iron stores in patients who are receiving transfusions. Olivieri and her colleagues also reported that deferiprone may accelerate the progression of hepatic fibrosis, in accord with studies in animals showing that this class of compounds, the hydroxypyridinones, may accelerate the progression of hepatic and cardiac fibrosis.[3]

In their editorial, Kowdley and Kaplan fail to acknowledge that for thalassemia, unlike genetic hemochromatosis, deferoxamine therapy is the gold standard and that accelerated progression of hepatic fibrosis does not usually occur in patients who are treated adequately with deferoxamine.[4] Kowdley and Kaplan suggest that deferiprone-treated patients were at risk for hepatic fibrosis because they had initially high hepatic iron concentrations, but in the study by Olivieri et al., the progression of fibrosis was greatest in patients with relatively low hepatic iron concentrations. The editorialists questioned the validity of the histologic assessment of relatively small liver-biopsy specimens. However, the use of these small biopsy specimens may actually have led to an underestimation of the degree of hepatic fibrosis. They also suggested that HCV caused the accelerated hepatic fibrosis. Although this may be so, the rate of progression of fibrosis in patients infected with HCV was slower in other studies than in the study by Olivieri et al.

Whether deferiprone can prevent iron-induced heart disease is unknown. What is now required is a prospective, randomized, controlled trial comparing deferiprone with deferoxamine and involving a large number of patients who would be willing to participate despite knowing that accelerated progression of fibrosis could occur and could have serious implications. Given the lack of other orally active agents and the problems and expense associated with deferoxamine therapy, particularly in developing countries, such a trial, if carefully monitored and preceded by adequate preclinical studies of toxicity, may be justified.

The data of Olivieri et al. were disputed by the corporate sponsor and its supporters[5] but were subsequently corroborated by others.[1,6] Olivieri et al. reported their findings under the threat of legal action by Apotex, the company that sponsored the trials, while at the same time receiving little support from their academic institution. Though therapy with deferiprone has a potential role in developed countries, its main value would be in poorer countries, where facilities for monitoring blood counts and performing repeated liver biopsies are extremely limited. Hence, it is all the more important to ascertain the potential toxicity of deferiprone and to determine its capacity to prevent iron overload before widespread use of this drug is encouraged in parts of the world where it would be really needed.

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1. Hoffbrand AV, Al-Refaie F, Davis B, et al. Long-term trial of deferiprone in 51 transfusion-dependent iron overloaded patients. Blood 1998;91:295-300.
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To the Editor: Olivieri et al. express concern that deferiprone may cause progressive hepatic fibrosis in patients with thalassemia major. We studied 20 patients with thalassemia major who had serum ferritin concentrations ranging from 1500 to 3000 μg per liter. Ten were treated with deferiprone (mean serum ferritin concentration, 2151± 648 μg per liter), and 10 were treated with deferoxamine (serum ferritin, 1950±720 μg per liter). The liver-biopsy specimens were evaluated according to the scoring system of Ishak et al.[1] by a hepatologist who was unaware of the patients' clinical status and treatment assignment. The mean degree of fibrosis was 1.44±1.01 at the start of treatment with deferiprone and 1.33±1.22 after a mean of 2.25±1.0 years of treatment. This difference was not statistically significant ($t=0.55$, $P>0.5$). In the deferoxamine group, the mean degree of fibrosis was 2.25±1.4 at the start of treatment and 2.12±1.55 after 2.20±0.96 years of therapy. This difference was also not statistically significant ($t=0.55$, $P>0.5$). When we compared both groups at the end of treatment, there was no significant difference between groups in the degree of fibrosis ($t=-2.38$, $P=0.05$). In the deferiprone group, the hepatic iron concentration was 1140±547 μg per gram of liver, dry weight, at the start of treatment and 3072±2421 μg per gram of liver, dry weight, at the end of treatment ($t=-2.36$, $P=0.05$). Our results suggest that deferiprone may not be involved in the evolution of liver damage in patients with moderate hepatic iron overload.

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1. Ishak K, Baptista A, Bianchi L, et al. Histological grading and staging of chronic hepatitis. J Hepatol 1995;22:696-9.

To the Editor: Olivieri et al. conclude that "deferiprone does not adequately control body iron burden in patients with thalassemia major" because 7 of 18 patients in their study had hepatic iron concentrations of at least 80 μmol per gram of liver, wet weight. Since the mean (±SE) hepatic iron concentration in these 18 patients fell from 88.7± 12.1 to 65.5±7.9 μmol per gram of liver, wet weight, during treatment with deferiprone and there was a significant decrease in serum ferritin concentrations, we find it surprising that Olivieri et al. consider the results of chelation with deferoxamine preferable to these results. Like Olivieri et al., we and others have shown that 75 mg of deferiprone per kilogram of body weight per day provides adequate chelation in a proportion of patients. For those in whom this dose is not adequate, a higher dose or a combination of deferiprone with small amounts of deferoxamine (amounts that are acceptable to patients) may substantially improve iron status.[1]

The authors do not state how many patients were positive for HCV RNA or whether any had been treated successfully with antiviral therapy. The effect of HCV clearly needs to be taken seriously in view of the fact that four of five patients (80 percent) with progression of fibrosis were HCV antibody–positive, as compared with two of nine patients (22 percent) without progression. In our study of long-term therapy with deferiprone, all five HCV RNA–positive patients had hepatic cirrhosis.[2] Among the 12 patients who were HCV RNA–negative, none had cirrhosis, 11 patients had no fibrosis, and 1 patient had mild fibrosis. Olivieri et al. have not proved that deferiprone causes hepatic fibrosis, and on the basis of their results, we cannot see the logic of the decision to discontinue deferiprone therapy in all patients. However, we agree that further prospective studies of deferiprone therapy are needed.

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Editor's note: Apotex recently supported one trainee sponsored by Drs. Wonke and Hoffbrand.

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2. Hoffbrand AV, Al-Refaie F, Davis B, et al. Long-term trial of deferiprone in 51 transfusion-dependent iron overloaded patients. Blood 1998; 91:295-300.

To the Editor: Olivieri et al. collected a lot of data during their seven-year study but included only selected values in their analyses. In some cases, only two of four points were considered. All available data should have been presented, so that the effect of any deviations could be assessed. For example, the stabilization of hepatic iron concentrations shown in Figure 2 of the article is not apparent in Figure 1.

Their finding of an absence of a significant difference between the initial and final mean hepatic iron concentrations ignores the fact that the concentrations decreased in 9 of 18 patients, were unchanged in 5 patients, and increased in 4 patients. Although the responses to deferiprone therapy and deferoxamine therapy may be similar in terms of urinary iron excretion, deferiprone therapy fails to result in a net negative iron balance in all patients.[1] The hepatic iron concentration is expected to rise in patients with a positive iron balance. Olivieri et al. chose to focus on a subgroup of seven patients whose final hepatic iron concentrations exceeded a threshold above which patients had an increased risk of cardiac disease and early death[2] and to suggest that this result was evidence of the loss of effectiveness of deferiprone therapy. In six of these seven patients, the hepatic iron concentration was presumably above the threshold throughout the study. Of these six patients, the hepatic iron concentration declined dramatically in four, was unchanged in one, and increased in one. This result is hardly evidence of diminished effectiveness. No evidence of a decrease in urinary iron excretion was pro-

vided. If the direction of the change in a value that is being serially evaluated is appropriate, the failure to breach a threshold simply means that the treatment should be continued. The same logic applies to serum ferritin. That 9 of 18 patients had final concentrations in excess of 2500 ng per milliliter does not provide evidence of either effective or ineffective chelation in a serial study.

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1. Grady RW, Hilgartner MW, Giardina PJ. Deferiprone: its efficacy relative to that of desferal. Blood 1996;88:Suppl 1:310a. abstract.
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To the Editor: The recent data on deferiprone reported by Olivieri et al. certainly dampen the previous enthusiasm of these investigators, who reported in 1995 that "deferiprone induces sustained decreases in body iron to concentrations compatible with the avoidance of complications from iron overload."[1] Even so, the new data are in keeping with the earlier findings of Olivieri et al.[2] and of Collins et al.[3] that the average change in iron excretion in response to deferiprone is sufficient to achieve a neutral iron balance. In other words, iron concentrations will increase in some patients, decrease in some, and remain stable in some during deferiprone therapy. The accuracy of this prediction is confirmed by the results shown in Figure 1 of the article by Olivieri et al.

Our thalassemia center, like most others, has some patients who steadfastly refuse to use deferoxamine regularly, although it is the only widely available iron chelator. In instances in which strong and repeated efforts by staff members to improve patients' compliance with deferoxamine therapy fail, it seems reasonable to be able to offer these patients the chance to stabilize or to reduce iron stores with deferiprone therapy, even if the resulting reduction is slow and the hepatic iron concentration remains above a threshold that is associated with an increased risk of complications. The argument for the use of deferiprone therapy is even more compelling for the small number of patients who are truly unable to use deferoxamine because of its unavoidable side effects.

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Editor's note: Dr. Cohen is an investigator in a safety trial of deferiprone sponsored by Apotex. Ms. Martin receives salary support from Apotex.

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The authors reply:

To the Editor: We are also concerned that thousands of children and young adults with thalassemia major may receive deferiprone — a drug that has been incompletely tested and that may harm rather than help them. Neither the preclinical nor the clinical evaluation of deferiprone has followed the customary pattern.[1] Instead, scores of limited and usually uncontrolled studies have been published. The sole animal study that met these standards (14 dogs were examined over a period of two weeks) was sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases.[1] Deferiprone has not even been evaluated in the gerbil model of human iron overload, in which a structurally similar hydroxypyridinone potentiates hepatic and cardiac fibrosis.[2] On behalf of Apotex, we designed and initiated a study of deferiprone that met the standards of good clinical practice and whose primary aim was to determine the incidence of drug-induced neutropenia over a one-year period.[3] The study included neither systematic serial hepatic biopsies nor formal cardiologic evaluations.

To our knowledge, the total number of children who are unable to use the standard iron-chelating agent, deferoxamine, in North America and Italy combined is less than a dozen. We think that if they were given the option of taking a safe and effective orally active iron-chelating agent, nearly all of these patients would be unwilling to undergo the discomfort of the almost nightly prolonged subcutaneous infusions that are required for the effective use of deferoxamine. We are concerned that patients and their physicians who are participating in "trials" or programs of "compassionate" use of deferiprone have not been adequately informed about the long-term lack of efficacy of the drug in many or most patients[4] and, more important, about the potential risk of damage to the liver and heart associated with this therapy. As we emphasized in our report, deferoxamine can protect against cardiac disease and, even in suboptimal doses, can arrest hepatic fibrosis.

The prevalence of HCV infection was similar in the two groups. In our deferoxamine-treated group, none of the patients — not even those who were HCV-positive — had progression of fibrosis (as shown in Table 2 of our article). It is known that the hydroxypyridinones accelerate hepatic and cardiac fibrosis in animals in the absence of HCV infection.[2,5]

In our view, any further studies to clarify the relation between deferiprone and tissue fibrosis should be conducted first in animals. If such studies show no evidence of hepatic fibrosis from the drug, then further clinical trials with this oral agent would be justified. Because the median time to progression of fibrosis was 3.2 years in our study, however, such trials must involve sufficiently long periods of observation, large numbers of patients, and careful monitoring of the drug's safety.

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To the Editor: Dr. Callea shares our concern about the adequacy of the liver-biopsy specimens in the study by Olivieri et al. and emphasizes the difficulty in drawing firm conclusions on the basis of such small specimens.

We agree with Nathan and Weatherall about the efficacy of deferoxamine. We stated in our editorial that deferoxamine is the "only drug proved effective in preventing iron overload in patients with thalassemia major." We also noted that the inconvenience, discomfort, and high cost associated with its administration limit its widespread use. Nathan and Weatherall seem unfamiliar with the importance of obtaining liver-biopsy specimens of adequate size. Had the liver-biopsy specimens been larger in the study by Olivieri et al., it would not have been necessary to speculate whether the use of small biopsy specimens may have led to an underestimation of the degree of hepatic fibrosis. Perhaps they did, but this was true only for the base-line biopsy specimens, not for the ones obtained at follow-up. If the liver-biopsy specimens had been of adequate size, there would have been no need to speculate about the severity of the pretreatment and post-treatment fibrosis.

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Diabetes and Coronary Heart Disease

To the Editor: Haffner et al. (July 23 issue)[1] have shown that diabetic subjects without prior myocardial infarction (mean age, approximately 58 years) have as high a risk of myocardial infarction as nondiabetic subjects with prior myocardial infarction. These findings were "population-based," according to the investigators, but they actually used a population register of diabetic subjects. We would like to report our observations in a cohort drawn from a true cross section of the population.

The Dubbo Study is an ongoing prospective study of cardiovascular disease in a cohort of elderly Australian subjects (mean age, approximately 70 years) who were first evaluated in 1988–1989.[2,3] Subjects were classified as having diabetes if they had previously received a diagnosis of diabetes from a physician, if they were using medication for diabetes, or if they had a single fasting plasma glucose level of at least 7.8 mmol per liter. The remaining subjects were considered to be nondiabetic if the fasting plasma glucose level was less than 6.1 mmol per liter. Because of the age of the population, cases of diabetes were predominantly type 2. Documentation of prior coronary heart disease was based on positive responses to a myocardial-infarction questionnaire or the Rose angina questionnaire or on diagnostic electrocardiographic changes.[2] Incident coronary-heart-disease events were hospital admissions with any manifestation of coronary heart disease (*International Classification of Diseases, 9th Revision, Clinical Modification* codes 410 through 414).

TABLE 1. INCIDENCE OF CORONARY HEART DISEASE (CHD) IN DIABETIC AND NONDIABETIC SUBJECTS.

PRIOR CHD	NONDIABETIC SUBJECTS		DIABETIC SUBJECTS	
	NO. OF SUBJECTS	NO. OF CASES (PER 100 SUBJECTS)	NO. OF SUBJECTS	NO. OF CASES (PER 100 SUBJECTS)
No	1941	20.1	130	31.5
Yes	478	52.7	77	72.7

In a five-year follow-up analysis of the cohort, overall mortality was twice as high in diabetic subjects as in nondiabetic subjects, among both men and women, and the incidence of coronary heart disease was two times as high in diabetic men and three times as high in diabetic women.[3] We have now completed 98 months of follow-up for coronary heart disease; the key findings are presented in Table 1.

Cox proportional-hazards models were used to compare the risk of coronary heart disease in subjects who had diabetes but no prior coronary heart disease with the risk in nondiabetic subjects with or without prior coronary heart disease. The models were adjusted for age, sex, and other cardiovascular risk factors.[2,3] The hazard ratio was 0.67 (95 percent confidence interval, 0.46 to 0.97; $P<0.04$) for the comparison with nondiabetic subjects who had prior coronary heart disease and 1.43 (95 percent confidence interval, 1.00 to 2.03; $P<0.05$) for the comparison with nondiabetic subjects who did not have prior coronary heart disease.

Our findings confirm the overall increased risk of coronary heart disease in patients with type 2 diabetes. However, the relative risk for diabetic subjects without prior coronary heart disease is still significantly lower than that for nondiabetic subjects with prior coronary heart disease. Differences between the findings reported by Haffner et al. and our findings may be related to differences in the selection criteria for the study populations, the definition of diabetes, the age and size of the groups, and the different end points (myocardial infarction in the study by Haffner et al. and coronary heart disease in our study).

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1. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229-34

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CORRESPONDENCE

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The Olivieri Case

To the Editor: In their article on the dispute over the iron-chelating agent deferiprone (Oct. 24 issue),[1] Nathan and Weatherall focus on the ethical implications for the relationships among scientists, their institutions, and industry. Their article ignores recent evidence on the safety and efficacy of the drug[2,3,4,5] and does nothing to resolve the uncertainty that has made deferiprone unavailable to the majority of patients with thalassemia worldwide.

This very public controversy has generated fear, uncertainty, and doubt among such patients and their physicians, fomented mistrust among clinicians and researchers, and undermined patients' confidence in their doctors. Such doubts have been heightened by the high respect in which North American science is held. The Food and Drug Administration has not licensed deferiprone, since its decisions are made in a North American context and cannot remain uninfluenced by such a high-profile dispute. Consequently, regulatory authorities in many countries have also declined to license deferiprone. As a result, although it has been used safely by thousands of patients for as long as 10 years and is marketed cheaply by Cipla in India, doctors in neighboring countries have been unable to use it, despite the fact that it offers the only hope for their patients with thalassemia. For every year this situation continues, at least 2000 to 3500 patients with thalassemia who receive regular transfusions die worldwide from untreated iron overload — more than the total number of such patients living in North and South America combined. Patients cannot wait 10 years for a better iron-chelating agent. They need deferiprone now because it is affordable, tolerable, and adequately safe and effective.

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To the Editor: Nathan and Weatherall misrepresent facts related to Apotex and deferiprone. Moreover, one of the authors failed to disclose his relationship with a company that is developing a competing drug[1] and, in so doing, violated recent *Journal* guidelines for authorship and accountability.[2] We take issue with many of the statements made by Nathan and Weatherall.

The facts as seen by Apotex are as follows. In 1992, Olivieri and a coinvestigator requested that Apotex support the development of deferiprone (L1), advocating the need for this oral drug in treating iron overload in patients with thalassemia major. Although it was needed by patients, deferiprone would not be viewed by a pharmaceutical company as a profitable investment because there are fewer than 700 patients with thalassemia major in the United States, there is a risk of agranulocytosis, and there would be patent protection for only a short time. Notwithstanding these limitations, Apotex made a commitment to develop deferiprone because of its potential for enhancing the survival of a segment of the population of patients with thalassemia major.

In 1993, Apotex initiated a program to determine the safety and efficacy of deferiprone, leading to its evaluation in more than 800 patients in Europe, North America, and other parts of the world. In 1995, Olivieri and a colleague of hers in Toronto expressed concern about a loss of response in six of their patients.[3]

The scientists at Apotex reviewed the data and concluded that they did not support this interpretation. To obtain an independent assessment, Apotex distributed the raw data to all the other investigators studying deferiprone. The investigators were unanimous in their disagreement with Olivieri's interpretation. Apotex then convened an international committee of experts to review the raw data and Olivieri's interpretation. The committee concluded as follows: "Specifically, the Committee does not find a trend toward a loss of effectiveness of therapy in patients treated with L1 [deferiprone] on a long-term basis. There are no sudden, unexpected changes in regard to failure of therapy."[4]

By that time, Apotex had decided not to renew Olivieri's contract and discontinued the study in Toronto, while continuing the studies at all other sites. Nathan and Weatherall characterize the termination of Olivieri's contract as an attempt to stop her from divulging her views, but the systematic approach to disclosure and review demonstrates that such a perspective is invalid.

Three months after her contract had been terminated, Olivieri submitted an abstract for presentation at a scientific conference,[3] not disclosing that a review of the data had been conducted and that two committees had rejected her conclusions. Only after her contract had been terminated did she allege that the use of deferiprone might be associated with an increase in the risk of hepatic fibrosis.[5] We think these claims have been disproved.[6]

Nathan and Weatherall demonstrate a lack of current knowledge regarding the clinical safety of deferiprone, its efficacy, and its role in the treatment of thalassemia major. Readers who wish to learn about deferiprone may refer to recent reports from independent[6,7,8,9,10] and Apotex-sponsored[11] studies. Deferiprone, now approved in 24 countries, is the only lifesaving alternative for patients with thalassemia major who will not or cannot take deferoxamine and for whom no other treatment is approved; Nathan and Weatherall would deny them this treatment.

In addition, Nathan and Weatherall falsely contend that within "a few years" after Apotex stopped the trials, "two lawsuits totaling over $20 million were formally lodged against" Olivieri. At no time did Apotex initiate any lawsuit against Olivieri. The truth may be found in the records of the Court of Ontario. It was Olivieri who filed numerous lawsuits against those who disagreed with her actions, including other scientists, the media, and Apotex. As part of its defense, Apotex filed a counterclaim.

In summary, the record shows a picture remarkably different from that portrayed by Nathan and Weatherall. What is academic freedom, and what evidence can an author hide from a journal or the scientific community? Is it acceptable to suppress the fact that conclusions have been challenged, particularly when extensive peer review has resulted in the rejection of the author's conclusions? What are the responsibilities that accompany academic freedom, and how are the patients' interests best served? There is a responsibility that comes with the right to academic freedom, and that is the duty of full disclosure and scientific objectivity.

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The authors reply: As physicians who have cared for patients with thalassemia for more than 40 years, we completely understand the anxieties expressed by Mr. Constantinou and colleagues. They desperately want an effective oral chelator, so do we. It took many years of careful clinical studies to prove that deferoxamine can save the lives of patients with thalassemia.[1,2] Before patients and governments in developing countries give up this drug and accept deferiprone as an effective agent for treating thousands of patients, a long-term trial must be performed to prove that it can control body iron levels. Sadly, as we understand it, the only study of this kind was stopped by the manufacturers of deferiprone six years ago. Had it not been stopped, we would have this information by now; there are no shortcuts to assessing control of the slow accumulation of iron in patients with thalassemia.

Although the current Apotex lawsuit against Olivieri may be defensive, Spino and Tricta fail to mention that their company threatened her repeatedly with legal action if she publicized her concerns about the efficacy and safety of deferiprone and even threatened the American Society of Hematology in the same way if it allowed her to present her results at its annual meeting. Furthermore, if the company's advisors were so confident that Olivieri was incorrect and that body iron levels were being controlled, why did they immediately stop the trial? Had they not done so, or had they at least ensured that adequate data on iron levels were made available from the toxicity studies that were continued, we would now have this vital information.

Spino and Tricta also suggest that we are denying the drug to those "who will not or cannot take deferoxamine." Patients in whom deferoxamine results in adequate control of the level of iron accumulation should survive for a long time without cardiac or other complications.[1,2] We ask only that similar controlled data be collected for deferiprone. In fact, a recent, peer-reviewed article reviewing the field of chelation concluded, on the basis of currently available evidence, that deferiprone does not control iron accumulation in a substantial number of cases.[3] Although the more recent studies of toxicity and cardiac function cited by Spiro and Tricta are interesting, ultimately it is iron accumulation that kills patients with thalassemia. Very few "cannot" take deferoxamine on medical grounds; those who "will not" should be reminded of the uncertainty of the long-term efficacy of deferiprone.

Finally, Spino and Tricta call into question the objectivity of our review by suggesting that one of us has a conflict of interest, presumably because of recent work on an oral chelator manufactured by Novartis. We would remind them, however, that we first asked for adequately controlled trials of deferiprone in 1995[4] — long before this new agent was on the scene — and have asked many times since. We have never had a financial interest in Novartis (Novartis Oncology has made a grant to the Dana–Farber Cancer Institute for the development of kinase inhibitors for cancer; it has nothing to do with chelation research, and we are not supported by it).

Our review of the Olivieri case was written because we are concerned about problems at the interface between academia and industry and about the importance of open scientific debate and academic freedom.[5] The fact that Spino and Tricta choose to interpret the article as the expression of a wish on our part to deny patients lifesaving drugs suggests that our fears are well founded.

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Sir David J. Weatherall, M.D.
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Editor's note: Dr. Olivieri was a fellow with Dr. Nathan in the mid-1980s. Editors consider events that took place more than two years before publication to be immaterial with respect to conflicts of interest.

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Rapid Responses to:

EDITORIALS:
Julian Savulescu
Thalassaemia major: the murky story of deferiprone
BMJ 2004; 328: 358-359 [Full text]

Rapid Responses: Submit a response to this article

Rapid Responses published:

Seeking the truth on deferiprone: an orphan drug for a market worth hundreds of millions.

18 February 2004 [Next Rapid Response] [Top]

George J Kontoghiorghes, Director
Postgraduate Research Institute of Science, Technology, Environment and Medicine

Send response to journal:
Re: Seeking the truth on deferiprone: an orphan drug for a market worth hundreds of millions.

Email George J Kontoghiorghes

Sir, The editorial by Dr J Savulescu considers the use of deferiprone (L1 or 1, 2-dimethyl-3-hydroxypyrid-4-one) and denial of access to it in North America within the context of western medical ethics but ignores the problem in its global perspective, which is the premature death of thousands of thalassaemia patients in developing countries due to lack of iron chelating drugs [1,2].

The dispute of Dr N Olivieri and Apotex has little to do with how deferiprone has been invented and developed, but is related to the lucrative market of chelating drugs, which is estimated to be about $ 0.5 billion annual sales. There are many other academic and commercially based conflicts regarding deferiprone, deferoxamine and experimental chelators but these have not been exposed to the public [1-3]. Deferiprone has a unique history of orphan drug development and from the time of its invention (1981), survived all sorts of attacks from commercial and academic sectors. These events could be traced in the literature as long ago as 1982 [4]. Events prior to the dispute should also be examined. For example, how and why was the drug named L1 and later deferiprone? Why was the research on deferiprone terminated at the places of invention, development and original clinical trials? Why were there no publications on deferiprone between 1981 and 1985? Why was deferiprone assigned for 3 years to Ciba -Geigy (now Novartis), the producer of the competing drug deferoxamine? Why is the Greek company Vianex, which sells deferiprone at a lower price than Apotex, being sued?

The first clinical trials in thalassaemia major patients using deferiprone, which clearly established the efficacy of the drug, have been published in BMJ 17 years ago and not 15 years ago as suggested by Dr Savulescu [1,5]. Most of the expenses associated with the development of deferiprone were supported by the United Kingdom Thalassaemia Society, a charitable organization. Deferiprone could be provided to thalassaemia patients that are not currently treated in developing countries at least 10 times cheaper than its present price in the west [2]. A BMJ editorial in 1991 was entitled "oral iron chelation is here".

Irrespective of the various disputes, oral iron chelation is here to stay and deferiprone will be playing a leading role not only in the treatment of thalassaemia but also of other diseases.

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1] Savulescu J. Thalassaemia major: the murky story of deferiprone. Conducting life saving research properly and quickly is a moral imperative. Br Med J 2004; 328: 538-9.

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overload in thalassaemia and other conditions. Comparison of epidemiological and therapeutic aspects with deferoxamine. Drug Saf 2003; 26: 553-84.

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Competing interests: : GJK is the inventor of deferiprone or L1 or 1, 2-dimethyl-3-hydroxypyrid-4-one and chairman of the international committee on oral chelators (ICOC).

Seeking the truth on deferiprone: an orphan drug for a market worth hundreds of millions.

18 February 2004

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George J Kontoghiorghes, Director
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Send response to journal:
Re: Seeking the truth on deferiprone: an orphan drug for a market worth hundreds of millions.

Email: George J Kontoghiorghes

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Irrespective of the various disputes, oral iron chelation is here to stay and deferiprone will be playing a leading role not only in the treatment of thalassaemia but also of other diseases.

References:

1] Savulescu J. Thalassaemia major: the murky story of deferiprone. Conducting life saving research properly and quickly is a moral imperative. Br Med J 2004; 328: 538-9.

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Competing interests: : GJK is the inventor of deferiprone or L1 or 1, 2-dimethyl-3-hydroxypyrid-4-one and chairman of the international committee on oral chelators (ICOC).

Independence of local ethics review

9 March 2004

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Mark H Wilson, Health Research Associates
Ottawa, Canada

According to Savulescu one can only speculate about whether the ethics committee had been more pro-active and exercised its independent status, many of the problems arising from the Olivieri affair may have been avoided. (1) While Savulescu correctly notes that

Send response to journal: Re: Independence of local ethics review

Email: Mark H Wilson

research ethics committees or boards (REBs) are considered research subjects main advocate, we also need to be reminded of concerns about Canadian REBs.

First, ethics review can be dominated by the majority of committee members who are often colleagues who not only review each others research but are also employed by a hospital or university which has a vested interest in research. Second, inspections of REBs in 1995 by the national council of ethics in human research raised the concern that REB independence is threatened by an expanding commercial research climate.(2) A Canadian academic claims that one large Canadian university funds its entire research ethics office from a drug company sponsor which is particularly disconcerting when the company's research protocols are reviewed.(3) Third, a recent report which assessed the effectiveness of national governance arrangements observed that many REBs report to the university office promoting research which is a conflict of interest. (4) Finally, Health Canada has noted that serious conflicts of interest may exist within REBs and research institutions. (5)

These unresolved accountability issues are worrisome given recent insider reports of REBs violating ethical guidelines in academic teaching centres and hospitals.(6) Health Canada and the US Office of Health Research Protection have also recently raised concerns about an REB at a leading Canadian University for not informing research subjects of risks in various clinical trials.(7) Against this backdrop, grounds exist to doubt whether local REBs can play the pro-active and independent advocacy role that Saulescu hopes they might.

Savulescu has raised related concerns about the structure and function of local research review in other countries and has made the call to replace the local system with specialized regional ethics committees that have a more independent status.(8) That call and its underlying ethical rationale also resonate in the Canadian context.

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Competing interests: None declared

The disappearing patient

13 March 2004

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George Constantinou, Patient
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Send response to journal: Re: The disappearing patient

Email: George Constantinou

To the Editor of the BMJ.

The disappearing patient

Julian Savulescu (1) suggests that the ethical committee is the closest advocate for patients because "no one group has the responsibility for representing the interests of all people affected by thalassaemia". But patients have voices, there are many active Support Associations. and all concerned should keep in mind that the thalassaemia people of the 21st century are educated, married with children of their own, successful businessmen and women, scientists, doctors, active politicians, but above all very knowledgeable about the economics and politics of their treatment. The UK Thalassaemia Society (www.ukts.org) and the Cooley's Anemia Foundation (www.thalassemia.org) are among 52 national associations under the umbrella of the Thalassaemia International Federation (TIF) (www.thalassaemia.org.cy). TIF aims to forge a global "thalassaemia community" embracing patients, families, doctors and scientists. Its activities include biennial international meetings where scientific sessions and patients' and parents' sessions are held side-by-side.

The problem of deferiprone is far more serious for patients than Dr Savulescu visualises. Globally, approximately 43,000 children with a major beta thalassaemia are born annually, most in developing countries (2). Approximately 62% need regular blood transfusion to survive, but only about 13% of them have access to it. We estimate that Worldwide over 72,000 patients are living on regular transfusions. Without iron chelation therapy they will die from iron overload between 12 and 24 years of age (3). However less than 50% of transfused patients have access to any form of chelation therapy, and probably only 10% (including the less than 1,000 patients resident in North America) benefit from the full protocol (4). Consequently, two to four thousand patients die annually from iron overload. The Olivieri debate contributes to these deaths by subordinating medical to political issues, and imposing a narrow North American perspective on a global problem. We find it hard to understand that a hospital ethics committee in a country which barely appears on the global map of thalassaemia can be

expected to make decisions with such important Worldwide consequences.

Available iron chelating agents

Most people with thalassaemia over 16 years of age owe their continuing survival to desferrioxamine, which became available in 1964. Its main problems are cost (about $10 per gram) and intolerability. Young children need 300 grams/year and adults need over 1 kg/year, so cost rises from $3,000 to over $10,000 per patient per year, making treatment completely out of reach for patients in developing countries. In Pakistan, where about 4,800 affected children are born annually (2), the Fatimid Foundation (a charity dedicated to voluntary blood donation) has provided regular transfusions for thousands of patients since the mid 1980s but cannot afford desferrioxamine. In Malaysia the Ministry of Health refuses to supply desferrioxamine until a thalassaemia prevention programme is in place.

When it is available, desferrioxamine is taken by subcutaneous infusion using a portable syringe-driver. Deaths from iron overload continue, mainly because many adolescents and young adults find "the pump" intolerable (5,6). Techniques used at expert centres to improve acceptability (implantable infusion devices, home-delivery of prepared disposables, psychotherapy) double treatment costs, and are not risk-free.

Despite these limitations the global market in desferrioxamine is worth hundreds of millions of dollars per year, and is growing. Desferrioxamine was one of Ciba-Geigy's top earners before it merged into Novartis: a switch to a cheaper chelator, or one not produced by Novartis, will obviously be unwelcome.

Deferiprone (L1) is a simple and potentially cheap oral iron chelator. The UK Thalassaemia Society supported its introduction for thalassaemia in the UK from 1987 at a total cost of £750,000 ($1,125,000). In 1992 TIF and its expert advisers requested Ciba-Geigy (then the only firm interested in iron chelation) to support clinical trials, largely because of the hope deferiprone offered for patients in developing countries. We were disappointed but not surprised when the firm declined in favour of developing a proprietary oral chelator. Without financial support for quality clinical trials, evidence would have to be collected piecemeal by dedicated professionals: the thalassaemia community seemed in for a bumpy ride – a prediction that has been amply fulfilled.

Apotex now produces deferiprone (as Ferriprox) for high resource countries under orphan drugs regulations. Cipla produces it (as Kelfer) far more cheaply in India, and many Indian patients have used it regularly for more than ten years, demonstrating that it can be sold at an affordable rate in developing countries. Though authoritative reviews conclude that its safety and efficacy is well within the usual range for commonly-used drugs (7), in many low-resource countries it is still not licensed, and so is not available to patients. This is (a) because it has not been licensed by the American FDA and (b) because of professional insecurity created by the Olivieri dispute. GC has been using desferrioxamine since 1972. At that time it was presented to him as an imperfect solution, that would permit survival until research provided a better treatment. Why should patients in developing countries not have the same opportunity with deferiprone?

We are not aware of a review supporting the opinion of Professors Olivieri, Nathan and Weatherall that "the safety and efficacy of deferiprone have not been established" (8), nor has any of them attended any TIF International Meeting since 1999 to engage in open scientific discussion in the presence of patients. For us the real question therefore is, how has the medical profession allowed an unsupported opinion to continue to dominate public and professional perceptions, as in Dr Savulescu's editorial?

The disappearing patient

When professionals become embattled, patients vanish from the picture - especially those who live in developing countries. When we responded to an article by Nathan and Weatherall (8) by pointing out that deferiprone offers the only hope of survival for thousands of patients who cannot afford expensive drugs (9) they replied "As physicians who have treated thalassaemia for over 40 years, we completely understand the anxieties expressed by Mr Constantinou and colleagues. They desperately want an effective oral chelator: so do we. It took many years of careful clinical studies to prove that deferoxamine can save the lives of patients with thalassaemia (10))". This response ignored our reasonable question of what these patients should do, and surprises us because (despite strong North American presence at TIF meetings) we do not know of any patient who names either author as their primary long-term carer. In addition, patients are barely mentioned in the Olivieri symposium (11). This succinctly demonstrates that in this particular case, as in any other similar occasions, conflict between the medical professionals, researchers and ethicists usually takes place in a utopian landscape where sight is lost of the single reason for the effort of doing research, namely benefiting the patients. Medical scientific research does not only harm patients if it is bad or slow (1), but also if it is a purely academic exercise or even worse a hostage between clinicians and corporations

Patients can help

In October 2003 we asked Professor Bernadette Modell to explain the present position to the hundreds of patients attending a TIF meeting in Sicily (12). She began with a public apology for the medical profession's failure to manage this problem, and explained four points (13).

1. Most doctors do not assess specialist literature themselves but rely on respected experts, who normally present their assessment in critical reviews. When such eminent individuals take sides in a controversy, their research colleagues must weigh the advantages and disadvantages for patients of antagonising authoritative figures who have the ear of medical editors, grant-giving bodies and the media. Most decide to keep their heads down and concentrate on obtaining the objective evidence that normally resolves

scientific disagreement. Fear of offending colleagues, being pilloried in the media and/or sued also play their part. But the patients' perception is that doctors who remain sitting on the fence are agreeing by default.

2. The consequent "silence" has bad effects. Patients feel they have dropped out of the picture altogether. Inability to obtain answers to reasonable questions increases their perception of being abandoned, leaves them vulnerable to rumour and misrepresentation, and greatly reduces their respect for their doctors. Among professionals, lack of openness creates mistrust and suspicion, aggravated by the anonymity of peer review. The sad truth is that the thalassaemia community has been poisoned. We are no longer honest with each other.

3. TIF has also been disappointingly silent. Although it very actively promotes the best patient care, it holds back from promoting the resolution of a conflict that works against patients' interests. Active promotion of desferrioxamine therapy (14) should be balanced with active promotion of a licensed alternative for patients who cannot access or cannot tolerate desferrioxamine therapy.

4. When professionals cannot retain objectivity they need help from patients, who have nothing to lose but their lives. We have the right to an open discussion that we can understand. We have the right to challenge opinions and ask authorities for their clinical credentials. We have the right to ask our Associations to support us and to publicise the results. Exercising these rights helps both professionals and patients. It is also facilitated by growing medical receptiveness to "expert patients" and to joint decision-making. Though some doctors may need to adjust to cope with these developments, any person who has, or who cares for someone with, a chronic condition is entitled to, and indeed should, share responsibility by negotiating their treatment options rather than merely obeying orders. This applies both for individual patients and for the patient community.

To take a positive view, our present disillusionment with the medical profession may represent a painful but salutary coming of age. We hope it marks the beginning of a more equal relationship that can help communities to cope with the growing market pressures within medicine. We do not believe that new regulations, including further involvement of ethical committees, can help in such complex and fluid situations. We expect our doctors "to cure sometimes, to relieve often, to comfort always" and believe that to do so, they need closer collaboration with patients.

What next?

Novartis now has a new oral iron chelator (ICL670) undergoing clinical trials (14). It would not surprise us if many researchers gladly put the murky issue of deferiprone behind them and move on, with adequate financial support, to investigate a new drug unlikely to involve them in conflict. But if ICL670 proves to be safe and effective will it be any cheaper than desferrioxamine, since Novartis is competing with itself? Unless it is much cheaper, deferiprone remains the only option for patients in developing countries – who will ensure that it is accessible for them?

As we see it, the deferiprone story has brought out many weaknesses of the medical research system, and of the human beings who work within it. Its message for the developing world is both depressing and challenging. It reflects the inexorable economic laws that govern drug firms, the difficulty of disentangling scientific, personal and commercial issues, and the neglect of all patients in developed and developing countries.

In the meantime, the fate of patients with thalassaemia in developing countries is a continuing tragedy, about which we in the developed world may feel deeply ashamed.

George Constantinou (aged 45 with thalassaemia major) UK Thalassaemia Society Committee Member, Past President of the Thalassaemia International Federation.

Stavros Melides (father of Vasos Melides with thalassaemia major), UK Thalassaemia Society Regional Liaison Officer and Assistant Secretary of the Thalassaemia International Federation.

Christos SOTIRELIS PhD. BEng(Hons) (Aged 39, Thalassaemia major) Air Transport Consultant

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Competing interests: None declared

Response to Savulescu Editorial. RE: Deferiprone

19 March 2004

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16 March, 2004

Send response to journal: Re: Response to Savulescu Editorial. RE: Deferiprone

Email A. Victor Hoffbrand

Editor - Julian Savulescu states in his Editorial1 "We still do not know whether deferiprone harms or benefits people with thalassaemia compared with deferoxamine". Doctors now prescribe deferiprone in 32 countries where it is licensed for treating thalassaemia major patients not adequately chelated by desferrioxamine. Published data clearly show it safely removes iron from a substantial proportion of patients for whom desferrioxamine proves, for one reason or another, inadequate.2 When Olivieri and colleagues subsequent 1998 paper appeared suggesting that the drug caused liver fibrosis3, the evidence for this toxic effect was immediately criticised on scientific grounds.4,5 Subsequent review in a blinded fashion of the same biopsies did not support fibrosis as a side effect of deferiprone.6 Three year follow-up biopsies in 56 patients found no evidence for liver fibrosis induced by the drug.7 No other scientifically reviewed study has reported this complication.

Uncertainties in the use of the drug that have arisen since 1998 are largely due to failure of separation of scientific evidence of the efficacy and side-effects of deferiprone from ethical issues arising from the dispute that arose between Olivieri and Apotex.

Recent, albeit retrospective, studies suggest that deferiprone may be superior to desferrioxamine for removing iron from the heart8,9 although at usual doses it may be less effective at removing liver iron.3,8 On the basis that deferiprone at 75mg/kg/day may indeed not be sufficiently powerful in all thalassaemia major patients to reduce liver iron to below 15mg/gram, a level that has been suggested to be associated with cardiac damage, efforts have been made to increase the proportion for whom it is effective. Doses up to 100mg/kg daily further increase iron excretion.10 Longer term safety studies at these higher doses are in progress and so far seem satisfactory. Also combined deferiprone and desferrioxamine therapy results in substantial iron excretion for patients in whom one or other drug is ineffective.10

It is now clear that deferiprone alone or in combination with desferrioxamine, is beneficial in a large majority of thalassaemia major patients with only a small minority of patients suffering well-recognised but reversible side-effects, such as arthralgia or agranulocytosis.2 Desferrioxamine and deferiprone should not be seen as rivals as Savulescu implies but as complementary in the management of patients with thalassaemia and transfusional iron overload.

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Yours sincerely,

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Competing interests: None declared

To the Editor

1 April 2004 Previous Rapid Response Top

Nancy F Olivieri, Professor of pediatrics and medicine
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Send response to journal:
Re: To the Editor

Email: Nancy F Olivieri

Many respected scientists and doctors in the thalassemia field are sympathetic to the confusion and frustration over the deferiprone controversy that was recently expressed by some patients 1. Like soldiers fighting for their country in an ill-advised war, many patients have been provided an ideology about deferiprone based upon 'facts' that are unproven, and opinions that remain resolute in the face of increasing evidence that deferiprone may not be adequately effective or safe in many patients 2, 3 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14. Patients cannot be faulted for believing that there exists "insufficient evidence" against the use of deferiprone as a substitute for deferoxamine, because there has been no shortage of perspectives 15 promoting that view. The patients' conclusion is understandable: "The fate of patients with thalassaemia in developing countries is a continuing tragedy about which we in the developed world may feel deeply ashamed."

No patients can be blamed for misunderstanding this situation. It is their advisors who should, indeed, feel deeply ashamed for misleading patients about the true priorities for thalassaemia management, and for having advanced the position that poor patients in developing countries have a 'right' to cheaper, potentially less effective medicine. There is considerable irony in the position of such advisors whose patients have enjoyed their prolonged survivals only because of decades of treatment with deferoxamine. Some physicians may not understand that they bear responsibility to help patients in the developing world gain access to equally safe and effective treatment. Instead, what many seem to emphasize is an apparently inalienable right of those dispossessed patients to be exposed to risks that richer patients do not need to take.

In a review by three of the most vigorous proponents of deferiprone it was, at last, conceded that during deferiprone therapy iron stores "decrease in some patients, remain stable in others, and increase in some others" 15, the same conclusion to which the manufacturer of deferiprone (Apotex), responded with legal threats and the premature termination of a prospective randomized trial, eight years ago 16. Despite repeated pleas17 for the large controlled trials needed to investigate this observation, those trials were never conducted; even in their absence there is now sufficient, indeed overwhelming, evidence against the use of deferiprone as a substitute for deferoxamine 2, 3 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 -- some arising from the very doctors to whom many UK patients entrust their care 2. It is indisupted that during long-term deferiprone many patients maintain body iron burdens above the threshold for premature death. Although some investigators 15 have made efforts, post hoc, to distance themselves from those original observations 2, their data (including a 10% death rate on deferiprone) have never been retracted. And as even its advocates note15, deferiprone's 'protective' effect on the iron-loaded heart must be viewed with caution: the endpoints promoted in studies of this issue remain unvalidated 18.

The 10% rate of death in deferiprone-treated patients reported by the London group 2 is sharply contrasted to the experience a few miles away at University College Hospital, where deferoxamine is prescribed and where there has been no death in any deferoxamine-treated patient born after 1974 19. This is consistent with prior reports over twenty years demonstrating the remarkable survival and prevention of heart disease during deferoxamine 20, 21, 22, 23, 24, 25, 26, 27, 28. As for the claim that deferiprone does not accelerate liver damage in selected patients, this has been undermined by the inexplicable exclusion, from that publication29, of previously recognized8 evidence of rising body iron stores30, as well as by evidence of hepatocellular damage13, and progression of liver fibrosis in more small cohorts,7,12 during deferiprone exposure. Because the relationship between liver fibrosis and iron is a complex one, prospective controlled trials were suggested when sentinel concerns were raised29; seven years later, such trials are still awaited, and these concerns are not allayed.

Perhaps what might assist patients is an appreciation that many arguments advanced in this controversy are self-contradictory or otherwise unsubstantiated. For example, a preliminary communication cited by 'The disappearing patient' 1 allegedly claims that high numbers of patients with thalassemia die, despite deferoxamine treatment 31. Not cited is a report by the same authors in the peer-reviewed literature exactly one year later 28, in which, in the large Italian study of patients receiving deferoxamine"the prevalence of heart failure at age 15 years decreased from 5% in patients born between 1970 and 1974, to 2% in patients born between 1980 and 1984". Another paper cited 32 has purported that the risk of death during deferoxamine therapy was 50%. The discrepancy between a 50% death rate reported by these UK investigators 32 and the 2% rate of cardiac disease reported two years earlier in Italy28 is not explained. No wonder patients are confused: how deferoxamine became apparently 25-fold less effective in

under two years is not easily understood. If patients believe these data, they might be influenced to abandon deferoxamine – and many have -- in favor of inadequately-studied therapy.

The manner in which even the restricted European licensing for deferiprone was acquired deserves scrutiny. In 1999, I launched a challenge to the licensing of deferiprone by the EU. Although the European Court refused to consider the merits of my case (dismissing this on technical grounds) 33, it was only because I launched this challenge that I was able to learn how deferiprone came to be licensed so quickly on that continent. Documents now publicly available show that Apotex, in evidence sworn to the court, attacked my ethics and ability -- alleging that ineptitude on my part had rendered the pivotal Toronto trial non- interpretable, and that I had falsified data. (Dr. Bernadette Modell was flown to the Luxembourg court to contribute to Apotex's case). Apotex went on to plead that as a result of my alleged incompetence, the company should be permitted to avoid the legal requirement to submit all evidence from the trial in question. Believing the company's allegations, the European licensing body agreed. Later, because all source documents had fortunately been retained, an independent audit of the trial was able to show it to have been conducted professionally and honestly. This further confirmed what another independent review had concluded two years before: "Apotex developed and disseminated, post hoc, plainly self-serving rationalizations for terminating the trials that differed significantly from its own earlier statements as to why it terminated them" and that "attempts to discredit Dr. Olivieri had the effect of serving the interests of Apotex, an aspect of whose licensing submissions for deferiprone was an attempt to discredit her and to dispute the risks identified." 16.

During the hearing in Luxembourg in April 2003, a European Court judge did not fail to note the irony of attempts to extend deferiprone use in humans in "Old Europe" at the same time that the USA was demanding more studies in animals. The Court also discussed the growing evidence that deferiprone was being misused. Although deferiprone is licensed only for those "unable to use" deferoxamine – 12 such patients are reported in the literature -- the number of deferiprone tablets prescribed in Europe during the first full year of authorization was equivalent to 488 patient- years, and during the second year, to 1400 patient-years. Deferiprone is clearly being used beyond the category of patients "unable to use" deferoxamine, and is now administered 'in combination' with deferoxamine in patients (who are by definition "able to use" deferoxamine) -- although such 'combination therapy' is not approved under European licensing. If (as claimed) deferiprone safely controls body iron as a single agent, why does deferiprone require 'combination' with deferoxamine in the same patient? And if (as claimed) deferiprone does indeed safely control body iron, and is associated with improved compliance, why have there been many deaths 2, 5, 11, 10, 34 35 36, 37, 38, 39 in patients treated with deferiprone? Surely these issues merit not rhetoric, but careful study. It is hoped that such prospective, controlled clinical trials, including one of 'combination therapy' using valid endpoints, could be initiated, without drug company sponsorship within the North American Thalassemia Clinical Research Network.

As for North America, it is correct that the American FDA has not licensed deferiprone. Indeed, that agency has demanded more studies of the drug. No one person possesses the power to prevent the licensing of a drug by the FDA. This constraint does not deny deferiprone to any patient who supposes he or she "needs" it. In the US (and Canada and Europe) any patient may choose to embark on unlicensed therapy if he or she can identify a drug company willing to provide the drug and a physician willing to supervise its use. Several patients (many enrolled in a one- year trial begun in 1995) have received deferiprone under the supervision of one US physician 40, 41, 13, while others are receiving deferiprone therapy in Montreal.

The deaths and the extraordinary dropout rate, in excess of 50% 13 -- without published follow-up of those withdrawn from study -- are not the only concerns. Now, poor patients in emerging countries use deferiprone as first line therapy, based upon the restricted licensing in the EU which permits richer patients to use it only as a second line drug. Many consider this to be desirable because "more patients" are said to be able to "afford" deferiprone in "developing countries"-- opinions voiced by some doctors who visit but do not work in these countries. The truth is that most patients in many emerging countries can afford neither adequate deferoxamine nor full doses of deferiprone. The licensing of deferiprone has provided a drug 'of uneven efficacy and uncertain toxicity' 42 -- often at fractions of the recommended dose 43 -- to only the very few richest families, while relieving governments of their responsibilities to provide the best treatment to all their citizens. Furthermore, unlike the situation in richer countries, most centers in emerging countries are unable to monitor patients adequately to prevent the potentially fatal agranulocytosis and crippling joint disease associated with deferiprone therapy. The real solution, of course, is to work to convince these governments to provide the safest, most effective therapy to their citizens.

Drs. David Weatherall and David Nathan have been criticized1 for their absence from thalassemia meetings in the past few years. In fact, these physicians, building on their considerable hands-on clinical experience with thalassemia patients over decades, are actively creating programs of treatment for thalassemia in emerging countries, and supervising the North American Thalassemia Clinical Research Network -- thereby addressing the precise needs about which many patients are concerned. But this criticism does raise a question: why do many serious scientists reluctantly attend these meetings or, like these authorities, decline to attend at all? One wonders whether the influence of commercial sponsors, and the focus of some meeting agendas, could be factors in such decisions. Without the motivation of financial or career advancement, Drs. Nathan and Weatherall have undertaken to judge the soundness of data by factual criteria (not, for example, by friendship with individual patients), to treat medical research findings as open and shared rather than secretive or proprietary (such that publication cannot be opposed with legal threats), and to form conclusions only after safety has been, not while it is being, established. Adherence to these ethical beliefs is not always in evidence at these meetings, but these values are not abusive of patient autonomy – they are respectful of it. Without those standards, "patients' informed consent" is an empty term. Surely, most patients understand that such scientific rigor and honesty are ultimately

their greatest safeguards.

Finally, who is the 'disappearing' patient? Patients who have enjoyed the life-saving benefits of deferoxamine for decades have not disappeared. These patients can return to adequate deferoxamine should complications develop during forays into experimental therapy. Having themselves survived because of deferoxamine, some patients in rich countries seem to accept the denial of this drug to poorer patients. In contrast, many of my colleagues -- patients as well as doctors -- understand that we must organize solutions that represent the best interests of the patients in emerging countries, not only the financial interests of their governments. We do not agree that a drug is made better by being cheap. Such a belief will allow patients to truly 'disappear.'

It is unfortunate that Dr. Julian Savulescu's original editorial 44 confused the issues. While advancing 'scientific' arguments which are not his expertise, Savulescu bypassed the fundamental ethical issue of this controversy: the obligation to put the concern for patients' safety first. Appropriate large-scale efficacy and safety trials of deferiprone could have been sponsored by Apotex when concerns were first raised in 1995 and 1996. Surprisingly, Dr. Savulescu suggests that this responsibility was that of a lone investigator who was under legal threats from Apotex, a target of gag orders and dismissals by her hospital and of harassment and defamation from a dishonest powerful senior colleague, and without effective support from her university -- then in negotiations with Apotex for a multi-million dollar donation.16 Contrary to what Dr. Savulescu suggests, the urgent need is not for fast-tracked licensing of unproven drugs, but rather for patient protection, informed consent, truly independent drug trials, and the defense of academic freedom.

I join my colleagues 30 in urging doctors and patients to examine critically the data regarding deferiprone, with the help of individuals of integrity and independence 45, 17, rather than to accept opinions expressed in discussions at selected meetings (see 46.) Perhaps each of us will then better understand the moral responsibility we share for patients who are, by accident of birth, less privileged than we.

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Competing interests: None declared

Abuse of patients' rights in the name of research integrity

5 April 2004

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Send response to Journal:
Re: Abuse of patients' rights in the name of research integrity

Email Panos A Ioannou

Sir,

The editorial by Savulescu [1] and the response by Kontogiorghes [2] highlight the moral imperative of the research community to come to a quick consensus on the place of L1 (deferiprone or 1, 2-dimethyl-3- hydroxypyrid-4-one) in the treatment of iron overload in thalassaemia.

Deferiprone is probably unique among modern drugs in that its early development was almost entirely funded by a patients' support group, the UK Thalassaemia Society. What is not surprising, however, is the subsequent exclusion of the UK Thalassaemia Society from any decisions concerning the availability of deferiprone for patient use.

L1 clearly posed an immediate threat to desferal monotherapy of iron overload in the early nineties, prompting Ciba-Geigy, now Novartis, to acquire all rights for its commercial exploitation. Ciba-Geigy promptly proceeded to give L1 the "kiss of death" by pronouncing it in 1993 as unsuitable for patient use, after a questionable series of tests on non- iron loaded animals. However, the medical community was not intimidated by this pronouncement and studies on L1 in thalassaemia patients continued to expand. Dr Nancy Olivieri one of the first clinical researchers that recognised the potential benefits of L1 in reducing intracellular oxidative damage and cardiac damage [3,4], convinced Apotex to fund a series of pivotal clinical studies on L1. However, these studies were interrupted by a dispute over claims by Dr Olivieri for an increased risk of liver fibrosis in L1-treated patients. The dispute has continued to reverberate for nearly ten years, with Dr Olivieri appearing to stand up for patients' interests and research integrity, and against interference by drug companies in sponsored research. The only definite outcome of the dispute has been the spreading of confusion in the minds of many patients and clinicians over the use of L1 and the continuation of desferal monotherapy, with all its limitations.

Following a series of studies by other workers that failed to show any increased risk of liver fibrosis in L1-treated patients, L1 was approved as a second line iron chelator by the European Agency for the Evaluation of Medicinal Products, a decision that was promptly challenged by Dr Olivieri in the European Court of Justice. However, by its decision of December 18, 2003, the European Court of Justice rejected the case of Dr Olivieri. Undaunted by this decision, Dr Olivieri distributed widely a circular, dated January 13, 2004, apparently under the names of the Canadian Health Coalition and the organization of "Doctors for Research Integrity" in which she states:

"You will remember that the fundamental reason that the Olivieri- Apotex-Sick Kids Hospital-University of Toronto controversy began was the protection of patients in clinical trials..."

and then,

"Has harm resulted from the licensing of deferiprone? Yes. Several premature deaths in patients receiving this drug have been reported over the last five years; still others have occurred but have not yet been reported. Sadly, these patients have become fatal statistics in experiments using deferiprone therapy."

I have asked Dr Olivieri in private correspondence to clarify whether her circular was approved by representative bodies of the above two organizations and to justify her claim of "premature deaths" in the absence of any such published evidence in the scientific literature. In fact, in a publication by the International Study Group on Oral Iron Chelators in 1995 in which Dr Olivieri is a co-author, it is clearly stated that "There was no treatment-related mortality" in the deferiprone- treated group of patients [3].

Although I have not received a direct response from Dr Olivieri, I have received a response from Prof David Nathan on January 25th, 2004, apparently on behalf of Dr Olivieri, which I feel morally compelled to make public [5]. In his message, Prof David Nathan offers the following explanation:

"The premature deaths to which Dr. Olivieri has referred are published reports of patients who died in a very short time on L1."

One cannot help but wonder why such unsubstantiated claims are raised now by Dr Olivieri in a non-scientific circular, at a time when thousands of patients are being treated by L1 without any reports of such deaths and when evidence is mounting that L1 may actually be saving patient lives by its cytoprotective and cardioprotective effects.

"The murky story of deferiprone" is clearly far from over. Research integrity and the interests of thalassaemia patients are being abused. Thousands of patients are being condemned to desferal monotherapy, while many more cannot afford the costs of current chelator therapy. Savulescu may wonder whether this affair could have developed differently "if the ethics committee in Toronto had taken a proactive and independent role in attempting to resolve the scientific dispute between Apotex and Dr Olivieri in 1996." However, what is more important now is for the UK Thalassaemia Society, the Thalassaemia International Federation and other representative patient organizations to wrestle the initiative and work with the broad medical community towards a consensus on deferiprone at the earliest opportunity on the basis of the available evidence. Those that persist to abuse research integrity and the interests of patients will then do so at their own peril.

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Competing interests: None declared

THE TRUE ETHICS OF THE DEFERIPRONE DEBATE

5 April 2004

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Send response to journal:
Re: THE TRUE ETHICS OF THE DEFERIPRONE DEBATE

Email Michael Spino, et al.

Dr. J. Savulescu has risen above the crowd by resisting the temptation to blindly support a medical investigator in her attack against industry, when she alleged foul play. Dr. N. F. Olivieri purported that she had uncovered potentially dangerous information about a drug being developed by a company, and that company attempted to prevent the dissemination of her information. Dr. Savulescu's editorial entitled, "Thalassemia major: the murky story of deferiprone", concludes, "One can only speculate that this whole affair may never have happened if the ethics committee in Toronto had taken a proactive and independent role in attempting to resolve the scientific dispute between Apotex and Dr Olivieri in 1996."(1)

This was the exact request made by Apotex to the Chairman of the Ethics Committee. In a letter dated, March 15, 1996, Apotex wrote to him noting it did not agree with Dr. Olivieri's interpretation of the data and asked that the REB look into the matter. On March 25, 1996, the Chairman wrote back stating that the REB would not do this, and, without the REB ever having formally evaluated the issue, he ordered unwarranted changes in the Consent Form. The numerous ongoing difficulties in the conduct of the study, together with those changes, not supported by the other investigators, precipitated the termination of the study in Toronto, but not elsewhere. Had the REB evaluated the matter, it is most likely that they would have come to the same conclusion as did an international expert panel 2 months later when it stated that there was no basis to Dr. Olivieri's conclusions of loss of response(2).

Some may consider this matter as a disagreement simply between an investigator and a company, but that was not the case. The other investigators, studying deferiprone in their own patients, reviewed the data and all concluded that Dr. Olivieri's allegations, even based on her own data, were untenable. At the very least, this matter should have been treated as any other serious disagreement among investigators, with an independent assessment of the data, a request rejected by the chair of the REB. However, the posturing on this event was that Dr. Olivieri was a "whistleblower", an independent investigator fighting industry to protect patients against the avarice of industry (3); good copy for the press, but far from the truth. At no time did Apotex opt to compromise patient welfare for financial gain, but it was a message that was readily accepted by those who did not have access to the information, but were exposed to the extensive promotion employed by Dr. Olivieri in publicizing her case(4).

A few, otherwise discriminating scientists, still seem to readily accept Dr. Olivieri's allegations(5), but their lack of knowledge of the facts becomes evident in their erroneous accounts of the matter. The natural consequence of this misinformation is ill-founded conclusions, as recently revealed in the New England Journal of Medicine(6).

Of even greater concern is that a supposedly unbiased academic-based committee, such as that formed by the Canadian Association of Universities Teachers (CAUT), would

publish a report on the matter, having interviewed Dr. Olivieri and her supporters, but not the hospital, nor the university nor the company which she was attacking(7). It is little wonder that their treatise contains a myriad of errors. Their lack of correct information could not help but bias their view in formulating their conclusions(8). Yet the opinions of many of those involved in the discussion of the report from the Journal of Medical Ethics, to which Dr. Savulescu refers, relied upon this very document. Thus, the myth is perpetuated, unwittingly by some, because of reliance on unfounded, but highly publicized allegations.

In answer to Dr. Savulescu's other concern, "we still do not know whether deferiprone harms or benefits people with thalassemia compared with deferoxamine", we offer the total sum of the world's published literature on deferiprone. To date, there have been over 50 peer-reviewed published clinical studies on deferiprone in over a thousand patients as revealed in a Medline search(9). Among those, some are more positive than others, as would be expected with the study of any drug, but Olivieri's study in 18 patients (10)is unique by suggesting that deferiprone should not be used, even in patients for whom no other iron chelators are available. It is noteworthy that her publication was accompanied by a precautionary editorial (11) and followed by a series of letters to the editor contesting its conclusions (12), (13), (14), (15), (16), (17). To answer Dr. Savulescu's question, there is no lack of information upon which to draw a scientifically sound conclusion, but reiteration of conclusions from a single study with a flawed post-hoc retrospective analysis, has clouded the issue.

Deferiprone is currently approved in > 30 countries around the world. Yet Dr. Savulescu is correct again in stating that if deferiprone is more effective than deferoxamine (or more tolerable), needless lives have been lost in those jurisdictions where the approval has not yet been granted, especially in light of the cardiac benefits which have been reported (18), (19).

We know of no other orphan drug that has been as extensively evaluated for regulatory purposes, nor of a situation where a potential life-saving alternative for patients who failed the only other available treatment, is denied to patients because of allegations, largely rejected by the scientific community.

More studies are always desirable, for any drug, but the available data make it unconscionable to deny deferiprone as an alternative to patients at risk of early death. This is the true ethics of the matter.

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Competing interests: We are employees of the company that manufactures deferiprone