Toward optimizing the use of deferasirox: potential benefits of combined use with deferoxamine

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ABSTRACT

Patients with β-thalassemia require iron chelation therapy to protect against progressive iron overload and non-transferrin-bound iron. Some patients fail to respond adequately to deferoxamine and deferasirox monotherapy while others have side effects which limit their use of these drugs. Since combining deferiprone and deferoxamine has an additive effect, placing all patients into net negative iron balance, we investigated the possibility that combining deferasirox and deferoxamine would lead to similar results. We conducted 34-day metabolic iron balance studies in six patients in whom the relative effectiveness of deferasirox (30 mg/kg/day) and deferoxamine (40 mg/kg/day) was compared, alone and in combination. Patients consumed fixed low-iron diets; daily urinary and stool iron excretion were determined by atomic absorption. Red blood cell transfusions were given prior to each drug treatment to minimize the effects of ineffective erythropoiesis. Serial safety measures, hematologic parameters, serum chemistries, ferritin levels and urinalyses were determined. All patients were in negative iron balance when treated with deferoxamine alone while four of six patients remained in positive balance when deferasirox monotherapy was evaluated. Daily use of both drugs had a synergistic effect in two patients and an additive effect in three others. Five of six patients would be in negative iron balance if they used the combination of drugs just 3 days a week. No significant or drug-related changes were observed in the blood work-ups or urinalyses performed. We conclude that supplementing the daily use of deferasirox with 2 – 3 days of deferoxamine therapy would place all patients into net negative iron balance thereby providing a convenient way to tailor chelation therapy to the individual needs of each patient. *Clinicaltrials.gov identifier: NCT00738413*

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Introduction

Patients with β-thalassemia major require regular transfusion therapy to sustain life.[1,2] While such therapy effectively treats their anemia, the iron present in the hemoglobin of the transfused blood is retained in the body, since there is no physiological means of excreting it.[3] Iron accumulates primarily in the liver and spleen, and to a lesser extent in the heart, pancreas, and other organs.[4] This excess iron catalyzes the formation of reactive oxygen species,[5] which damage a variety of macromolecules and cell structures leading to hepatic cirrhosis, endocrine abnormalities,[2,6] cardiac disease[2,7] and eventually premature death.[7] The use of chelating agents has proven to be highly effective, being associated with reductions in both morbidity and mortality.[7-9] However, the available chelating agents have significant limitations. Deferoxamine (DFO), introduced in the 1960s, was the mainstay for more than 30 years. Regular use, with improved clinical management, essentially doubled the average lifespan of patients.[8,10] Unfortunately, DFO must be given parenterally, the most effective regimens involving daily subcutaneous infusion over 8 to 12 h, at doses of 40 to 60 mg/kg/day.[2,4,11,12] Needless to say, lifelong adherence is problematic with few patients getting the maximum benefit from their use of DFO.[13]

To overcome this hurdle, attempts to develop safe and effective oral agents have been ongoing since the mid 1970s.[3,14-16] The first candidate to receive regulatory approval was deferiprone (DFP). It is generally recommended that this drug be taken at doses of 75 to 100 mg/kg/day in three divided doses, 5 to 7 days a week.[17,18] While DFP is not as effective as DFO in most patients,[19] adherence to its use is somewhat better.[7,8,20] With prolonged use, it is quite clear that body iron load is reduced and cardiac function is improved.[7,8,21] It does, however, have side effects that limit its usefulness. Chief among these are musculoskeletal (arthralgia, arthropathy), gastric (nausea, vomiting) and hematologic (neutropenia, agranulocytosis) effects.[22,23] Thus, up to 30% of patients discontinue its use for one reason or another.

In an effort to optimize the use of DFP, we conducted a series of metabolic iron balance studies to evaluate its relative effectiveness, alone and in combination with DFO.[24-26] These studies demonstrated that iron excretion varied widely at all doses of DFP (50, 75 and 100 mg/kg/day) and DFO (40 and 60 mg/kg/day) evaluated, and that not all patients were in net negative iron balance when taking DFP alone, even at a dose of 100 mg/kg.[25,26] On the other hand, combination therapy, employing the same dosing schedules used when studying the individual drugs, placed every patient in net negative iron balance at all

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combinations studied.[25,26] Overall, the results suggested that a variety of dosing schemes would achieve the levels of iron excretion needed to eliminate iron overload while minimizing side effects. Subsequent long-term clinical studies have substantiated these expectations.[9,27-33]

The approval of deferasirox (DFX) as an orally effective iron-chelating drug in 2005 promised to improve the management of iron overload as this drug could be taken once daily and apparently had few side effects.[34,35] Moreover, it proved to be non-inferior to DFO in a large, multicenter, randomized controlled trial involving roughly 600 patients; the doses of DFO and DFX ranged up to 60 and 30 mg/kg/day, respectively.[36] Many patients subsequently switched to DFX. Significant reductions in body iron load were achieved[37-40] with some patients showing improvement in cardiac function.[39] However, it is clear that DFX has its own limitations. While a wide variety of side effects have now been observed, it is primarily gastrointestinal and renal disturbances that limit the use of this drug in some patients.[37,38] In addition, a number of patients exhibited rising serum ferritin levels suggesting that net negative iron balance was not being achieved.[41,42] Based on our previous studies, we speculated that supplementing the use of DFX with one or more days of DFO therapy would lead to net negative balance in all patients. Accordingly, we undertook a metabolic iron balance study in which the relative effectiveness of DFX and DFO was compared, alone and in combination, with each patient serving as his/her own control.

Design and Methods

Patients

Six patients (2 males/4 females) with β-thalassemia major, 27 to 34 years of age, were recruited from the Ospedale Regionale Microcitemie, Cagliari, Sardinia, Italy. The patients selected for the study were drawn from a larger pool of eligible patients based on their availability and willingness to travel to New York City as well as an assessment of their preparedness for the rigors of a 34-day stay in our metabolic research unit. Their weight, yearly transfusion requirement, screening serum ferritin level, hepatitis C virus status and hemoglobin level upon admission are presented in Table 1. None of the patients was splenectomized. Their most recent chelation regimens were daily DFX (one patient), daily DFP (three patients), and daily DFP supplemented with intermittent subcutaneous infusion of DFO (two patients). None of the patients had a history of clinically significant gastrointestinal, renal, hepatic, endocrine, oncologic, infectious, pulmonary or cardiovascular disease, other than conditions associated with β-thalassemia and/or iron overload, such as compensated cirrhosis, endocrine insufficiency and diabetes. Moreover, no patient had a history of tuberculosis, epilepsy, psychosis, glaucoma or any other condition, which in the opinion of the investigators, would jeopardize the safety of the patient or affect the validity of the study results. None was positive for human immunodeficiency virus or being treated for hepatitis C. The study (NCT00738413) was approved by the Institutional Review Board and the Scientific Advisory Committee of the Weill Cornell Medical College. Written informed consent was obtained from each patient. All travel-related expenses incurred by the patients as well as all costs related to the 34-day hospital stay were paid for by research grants. The patients received no compensation for their participation.

Study design

This metabolic iron balance study involved a 34-day stay in our Clinical Research Unit, a component of the Clinical and Translational Science Center. Three 6-day drug dosage periods were preceded and followed by a 4-day washout. The duration of the washout periods was chosen to include the gastrointestinal transit time of most patients with thalassemia. Throughout the study, the patients consumed a fixed low-iron diet (11-15 mg of iron/day) consisting of four rotating meal plans designed by our nutritional staff in consultation with the individual patient. The patients could choose whatever they wished to eat, the iron content of the meals being regulated by portion sizes. Each meal plan contained 50% more calories than needed according to the individual's body mass index. The patients were not, therefore, expected to consume all of the food provided. All uneaten food was collected and its iron content determined to assess the amount of iron excreted. A unit of blood was given on days 1, 11, 21 and 31 to ensure that the hemoglobin level/degree of erythropoiesis was the same prior to each drug treatment.

DFO (40 mg/kg/day) was infused subcutaneously over 8 h at night during the first drug dosage period (days 5-10). On days 15-20, DFX (30 mg/kg/day) was given orally 30 min prior to breakfast. The combination of drugs was given on days 25-30, the dosages and dosing schedules being the same as those used previously. Twenty-four-hour collections of urine and stool were made each day, their iron content being determined by atomic absorption. Each bowel movement was collected and analyzed separately. A stool marker, Brilliant Blue, was given before the first dose of drug on days 5, 15 and 25, and after the last dose of drug on days 11, 20 and 31, to aid in assessing drug-induced stool iron excretion. Specimens of blood and urine were collected on days 1, 6, 10, 14, 16, 20, 24, 26, 30 and 34 for determination of safety measures. Serum analyses included measurements of sodium, potassium, chloride, bicarbonate, glucose, blood-urea nitrogen, creatinine, phosphorus, calcium, magnesium, uric acid, bilirubin (total), bilirubin (direct), protein (total), albumin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, copper and zinc.

Table 1. Patients' profiles.

Patient #	Sex	Age (years)	Weight (kg)	YTx[1] (units)	Hb[2] (g/dL)	Ferritin[3] (ng/mL)	HCV status	Spleen status	Most recent chelation regimen (mg/day x number of days)
1	F	27.2	34.6	39	9.3	1,100	Pos	Intact	DFX; 750x7
2	F	29.8	45.4	39	12.3	1,500	Pos	Intact	DFP; 3,000x7
3	M	29.7	57.2	52	13.0	1,650	Neg	Intact	DFP; 4,000x7
4	M	29.7	50.0	52	12.7	2,620	Pos	Intact	DFP; 4,000x7
5	F	33.8	46.0	62	12.9	7,860	Pos	Intact	DFP; 4,000x7 plus DFO; 2,500x3
6	F	32.8	41.1	39	12.1	2,320	Pos	Intact	DFP; 3,000x7 plus DFO; 2,000x5

[1]YTx: yearly number of transfusions; [2]Hb: hemoglobin level at time of admission; [3]ferritin: ferritin level at time of admission; HCV: hepatitis c virus.

Serum iron, the total iron binding capacity, transferrin saturation and ferritin were also determined. Hematologic parameters included a complete blood count with differential, reticulocyte and platelet counts. Urinalyses included a determination of protein, β_2-microglobulin, glucose, ketones, hemoglobin, pH, specific gravity and bacteria as well as creatinine and creatinine clearance (calculated). All of the analyses were carried out in the central laboratories of the New York Presbyterian Hospital. Physical examinations were conducted on admission and after each drug dosage period.

Determination of urine, stool and dietary iron

Complete meal plans were homogenized in deionized water (MilliQ). The homogenate was weighed and an aliquot (approximately 5 mL) was then placed in a tared porcelain crucible. The weight of the aliquot was determined after which it was dried overnight in an oven at 110°C. The dried residue was then ashed in a Muffle furnace (model 62700, Barnstead-Thermolyne Corp., Dubuque, IA, USA) at 550°C for 16 h. The ash was dissolved in 3 N HCl and the solution transferred to a 50-mL volumetric flask. The crucible was washed twice with 0.36 N HCl and the washings were added to the flask. The volume in the flask was brought to 50 mL with deionized water after which the iron content of the solution was determined by flame atomic absorption (model 3100, Perkin-Elmer Corp., Waltham, MA, USA). Uneaten food and stool specimens were treated similarly. The volume of 24-h urine specimens was measured and then a 3-mL sample was added to 9 mL of 0.6 N HCl. After standing overnight, the contents were centrifuged at 3000 rpm. The iron content of the supernatant was determined directly by atomic absorption. The urine, stool and residual food specimens were analyzed in duplicate, the complete meal plans in triplicate.

Determination of drug-induced urine and stool iron excretion

Drug-induced urinary iron excretion was determined by subtracting the mean daily excretion of iron during the washout periods from the mean daily excretion during the drug treatment periods. In order to take into consideration the gastrointestinal transit times and stooling patterns of each individual, net stool iron excretion was determined as follows. The total amount of iron excreted between the marked stools was calculated. The dietary iron consumed over the period of drug treatment was subtracted from this, the assumption being that dietary iron absorption was minimal in well transfused patients with β-thalassemia major. The resulting value was divided by the duration of drug treatment in days in order to determine the daily drug-induced excretion of stool iron.

Statistical methods

Given the small sample size and wide patient to patient variability, no attempt was made to assess the statistical significance of the differences seen. Simple means and standard deviations are presented. The excretion data are net values, taking into account iron excretion during non-drug days as well as the iron content of all uneaten food and the transit times of each individual. Iron balance was then calculated as the ratio of total net excretion to the amount of iron received in the form of transfused red cells, values greater than 100% representing negative iron balance. The effectiveness of combination therapy was assessed by comparing total net excretion in response to the combination with the sum of the observed excretions due to the individual drugs, values greater than 125% being deemed to indicate a synergistic response, those less than 100% a less than additive response. The effect of days of use was calculated arithmetically.

Apart from the issue of statistical significance, the small sample size and nature of the studies lend themselves to questions regarding reproducibility of the results. Given the duration and complexity of the studies, it was not feasible to evaluate this issue formally. Instead we have relied upon consistency. Over the course of more than 50 such evaluations of iron balance involving DFO as a comparator for four experimental drugs, the responses to DFO varied significantly, stool iron excretion ranging from 31% to 79% (mean 61%) of the total in individual patients. In 13 cases, the patient being studied had volunteered for the second or third time. In these patients the excretion patterns and total amounts of iron excreted were quite similar, the differences being less than 10% despite an intervening time of 2 years or more. Furthermore, when different doses of DFP were being evaluated, the excretion patterns in response to the latter drug were consistent from dose to dose, total iron excretion increasing with dose. Finally, in two patients three doses of DFP (50, 75 and 100 mg/kg/day) were compared over the course of the 34-day stay. Here, too, only the total iron excretion varied significantly, the percentage of stool iron remaining largely unchanged. Of added assurance, when one of these patients was studied again 2 years later, very similar results were obtained. Accordingly, we feel confident that our results accurately reflect the relative effectiveness of the drugs/drug regimens being compared.

Results

Safety measures

No significant, consistent or drug-related changes were seen in any of the safety measures assessed (*data not shown*). As expected, serum iron levels were generally higher than normal as were the levels of transferrin saturation. These values tended to fluctuate during drug administration with increases in some patients and decreases in others, undoubtedly reflecting a contribution from the iron chelation regimen being studied. The changes observed were not consistent from one drug regimen to another. The only other parameter that tended to fluctuate in response to drug administration was the level of serum zinc. Again, however, the changes lacked consistency. In two patients zinc levels tended to increase after beginning each drug regimen while in two others only DFO seemed to cause an increase. None of the other serum parameters evaluated appeared to change in a consistent or drug-related manner. Except for β_2-microglobulin, all of the urinary parameters measured were within normal limits and no consistent or drug-related changes were noted. β_2-microglobulin levels were high in two patients, very low in two and mid-range in the others with greater fluctuation seen in those with higher values. Most importantly, no evidence of increased toxicity was observed upon giving the drugs in combination, a finding that must be further assessed in dedicated long-term clinical trials.

Drug-induced iron excretion

Tables 2, 3 and 4 show the net mean daily amounts of iron excreted in urine and stool following administration of DFO (40 mg/kg/day), DFX (30 mg/kg/day), and DFO (40 mg/kg/day) plus DFX (30 mg/kg/day), respectively, for 6 days. The post-transfusion hemoglobin level together with the daily input of iron from transfusion therapy are also shown. The hemoglobin levels of each patient 3 days prior to the beginning of each drug regimen exceeded 11 g/dL, ensuring that absorption of dietary iron would not affect the results. Iron balance is defined as the ratio of the total amount of iron excreted to that received from the transfu-

Table 2. Iron excretion in response to DFO (40 mg/kg/day).

Patient #	Hb (g/dL)	Transfused Iron (mg/day)	Transfused Iron (μg/kg/day)	Urine Iron (mg/day)	Urine Iron (μg/kg/day)	Stool Iron (mg/day)	Stool Iron (μg/kg/day)	Total Iron (mg/day)	Total Iron (μg/kg/day)	Stool Iron (%)	Balance (%)
1	11.1	17.84	516	10.89	315	11.37	329	22.26	643	51	125
2	12.6	17.84	393	11.98	264	27.16	598	39.14	862	69	219
3	13.5	23.79	416	17.43	305	16.53	289	33.96	594	48	143
4	12.6	23.79	476	7.79	156	21.97	439	29.76	595	74	125
5	12.9	28.37	617	30.88	671	31.80	691	62.68	1363	51	221
6	12.8	17.84	434	12.61	307	17.95	437	30.56	744	59	171
Mean	12.6	21.58	475	15.26	336	21.13	464	36.39	800	59	167
SD	0.8	4.42	82	8.26	174	7.45	155	14.02	294	11	44

Table 3. Iron excretion in response to DFX (30 mg/kg/day).

Patient #	Hb (g/dL)	Transfused Iron (mg/day)	Transfused Iron (μg/kg/day)	Urine Iron (mg/day)	Urine Iron (μg/kg/day)	Stool Iron (mg/day)	Stool Iron (μg/kg/day)	Total Iron (mg/day)	Total Iron (μg/kg/day)	Stool Iron (%)	Balance (%)
1	11.0	17.84	516	0.03	1	10.94	316	10.97	317	100	61
2	12.6	17.84	393	0.27	6	22.74	501	23.01	507	99	129
3	11.7	23.79	416	0.21	4	10.56	185	10.77	188	98	45
4	11.5	23.79	476	-0.02	0	6.80	136	6.78	136	100	28
5	12.8	28.37	617	1.07	23	17.54	381	18.61	405	94	66
6	12.1	17.84	434	0.23	6	17.95	437	18.18	442	99	102
Mean	12.0	21.58	475	0.27	6	14.42	326	14.72	333	98	72
SD	0.6	4.42	82	0.43	9	5.94	143	6.14	147	2	37

sions. Expressed as a percentage, net negative iron balance is, therefore, any value exceeding 100%.

Iron excretion in response to DFO at a dose of 40 mg/kg was sufficient to place all patients into net negative iron balance (Table 2). In other words, iron excretion exceeded transfusional iron intake (125% - 219%). On a weekly basis, however, the effectiveness of DFO depends upon the days of usage. Thus, two of the patients (1 and 4) would not achieve net negative iron balance if they infused DFO only 5 days a week (Table 5). If used less frequently, a greater percentage of the patients would fail to maintain balance. With just 4 days of use, only two patients (2 and 5) would achieve negative balance while none would do so if the drug were used only 3 days a week. In agreement with earlier studies, approximately 60% of the iron excreted appeared in the stool.[11,25]

In a large randomized, controlled trial, the oral chelator DFX was found to be non-inferior to DFO at doses of 20 and 30 mg/kg/day.[36] Our results, comparing the relative effectiveness of the two drugs in the same patient, are somewhat different (Table 3). While taking DFX, patient 2 was in significant negative balance (129%) and patient 6 was just in balance (102%), but the other four patients remained in positive balance (<100%), meaning that their body iron load continued to increase, albeit at a slower rate. DFX (30 mg/kg) proved to be less effective than DFO (40 mg/kg) in all six patients, the relative effectiveness ranging from 23% to 60% (Tables 2 and 3). While two of the six patients would be in negative iron balance with daily use of the oral drug, none would achieve negative balance (20% to 92%) if using it only 5 days a week (Table 5). This result is not surprising considering that two of seven patients failed to achieve net negative iron balance when given DFX daily at a dose of 40 mg/kg/day in our previously reported balance studies.[43] As in earlier studies, nearly all of the iron excreted in response to DFX appeared in the stool.[34,41]

The results obtained upon giving the drugs in combination are shown in Table 4. Combining the drugs, using the same doses and dosing schedules as those employed when giving the drugs individually, resulted in a marked increase of iron excretion. If the iron excreted upon giving the combination is compared to the sum of the excretions when the drugs were given individually, this parameter was synergistic (more than 125%) in patients 1 and 4, essentially additive in three and less than additive in patient 2, the patient who responded best to DFX alone. In fact, five out of the six patients would be in net negative iron balance if they used the combination just 3 days a week with no chelation the other 4 days (Table 5). The excretion pattern mimicked the situation seen when DFO was given alone with roughly 60% of the iron excreted appearing in the stool. Individually, the percentage of iron in the stool increased approximately 20% in three patients, remained the same in two and decreased by approximately 25% in one (patient 4).

Discussion

Comparing the efficacy of iron chelators is different from comparing the efficacy of drugs used to treat diseases/disease symptoms because the former act stoichiometrically, with iron being constantly lost and gained. This difference is compounded by the high degree of variability among patients when evaluating the relative effectiveness of a given chelator. A number of factors, such as the effect of

Table 4. Iron excretion in response to DFX (30 mg/kg/day) plus DFO (40 mg/kg/day).

Patient #	Hb (g/dL)	Transfused Iron (mg/day)	Transfused Iron (μg/kg/day)	Urine Iron (mg/day)	Urine Iron (μg/kg/day)	Stool Iron (mg/day)	Stool Iron (μg/kg/day)	Total Iron (mg/day)	Total Iron (μg/kg/day)	Stool Iron (%)	Balance (%)
1	11.4	17.84	516	22.68	655	22.18	641	44.87	317	49	251
2	11.9	17.84	393	13.95	307	33.79	744	47.74	507	71	268
3	12.4	23.79	416	21.19	370	27.85	487	49.05	188	57	206
4	11.2	23.79	476	26.58	532	30.82	616	57.40	136	54	241
5	11.8	28.37	617	28.39	617	48.33	1051	76.72	405	63	270
6	12.1	17.84	434	14.04	342	33.64	818	47.68	442	71	267
Mean	11.8	21.58	475	21.14	471	32.77	726	53.91	333	61	251
SD	0.5	4.42	82	6.11	150	8.76	195	11.96	147	9	25

food on drug absorption,[44] ineffective erythropoiesis, splenectomy[45] and overall iron burden, contribute to such variability. In 2008, Cohen *et al*. showed that the rate of transfusion correlates with the effectiveness of DFX and DFO.[45] They found that negative iron balance was observed in a smaller proportion of patients as the rate of transfusion increased. For example, neutral or negative iron balance was found in roughly 80% (DFX) and 90% (DFO) of those who were heavily transfused, not unlike the proportions (67% and 100%, respectively) reported here. However, one cannot conclude from their data that the relative effectiveness of the two drugs in individual patients within similarly transfused groups would necessarily follow the same pattern. Individual eating habits (DFX), infusion rates (DFO) and tissue distributions as well as the aforementioned factors could affect the effectiveness of one or both drugs. While the factors cited undoubtedly influence patient-to-patient variability, they do not negate the important differences associated with comparing group means to the relative effectiveness seen in a specific patient. Despite patient-to-patient variability, and studies like that of Cappellini *et al*. our results lead us to conclude that, in most patients, infusing DFO daily is more effective than using DFX. The clinical results with DFX reported post-registration lend support to our findings. It appears that more than 30 mg/kg/day are required to achieve net negative balance in a substantial percentage of patients, as evidenced by the failure of liver iron and serum ferritin levels to decline appropriately over time.[41,42,46] Even at a dose of 40 mg/kg/day, however, not all patients achieve net negative iron balance.[43] Moreover, increasing the dose of the drug is problematic as evidence of toxicity has also increased.[47] The efficacy of DFX might also be increased by splitting the dose. Chang *et al.* reported that serum ferritin levels declined by nearly 40% in 11 patients, who were unresponsive to once daily doses of DFX, after treatment for 6 months with twice daily dosing, the total dosage being the same.[48] Further studies involving the measurement of iron excretion and non-transferrin-bound iron would be required to validate this approach.

With adherence to the use of DFO being a major issue in the management of β-thalassemia,[13,49] our results highlight the need for more patient-friendly chelation regimens. The issue, then, is how best to optimize the use of the oral agents. Our approach has been to supplement their use with limited infusion of DFO. This promises to increase iron excretion and, depending upon the results achieved, to allow for reducing the dose of one or both drugs in order to minimize toxicity, if observed. Thus, heavily iron loaded patients could benefit from a more rapid removal of toxic iron stores while those in whom such stores have been normalized could benefit from a maintenance regimen tailored to their particular needs/lifestyles.

The results reported here are similar to those we

Table 5. Iron balance (%) related to the frequency of drug administration.

DFO	7 Days	6 Days	5 Days	4 Days	3 Days
Patient 1	125	107	89	71	53
Patient 2	219	188	157	125	94
Patient 3	143	122	102	82	61
Patient 4	125	107	89	71	54
Patient 5	221	189	158	126	95
Patient 6	171	147	122	98	73

DFX	7 Days	6 Days	5 Days	4 Days	3 Days
Patient 1	61	53	44	35	26
Patient 2	129	111	92	74	55
Patient 3	45	39	32	26	19
Patient 4	29	24	20	16	12
Patient 5	66	56	47	38	28
Patient 6	102	87	73	58	44

SUM[1]	7 Days	6 Days	5 Days	4 Days	3 Days
Patient 1	186	160	133	106	79
Patient 2	348	299	249	199	149
Patient 3	188	161	134	108	80
Patient 4	154	131	109	87	66
Patient 5	287	245	205	164	123
Patient 6	273	234	195	156	117

COM[2]	7 Days	6 Days	5 Days	4 Days	3 Days	COM/SUM[3]
Patient 1	251	215	180	144	108	135
Patient 2	268	229	191	153	115	77
Patient 3	206	177	147	118	88	110
Patient 4	241	207	172	138	103	156
Patient 5	270	232	193	154	116	94
Patient 6	267	229	191	153	115	98

[1]SUM represents the additive effects of DFO and DFX monotherapy; [2]COM represents the effect of DFX plus DFO; [3]COM/SUM represents the percentage of additivity.

observed when studying the effects of combining DFP and DFO.[24-26] In these studies, some patients who exhibited evidence of synergy had a significant decrease in the percentage of iron excreted in their stool when given the combination of drugs. This led us to suggest that DFP could "shuttle" iron to DFO in the bloodstream for excretion in the urine, the free ligand then being available to chelate more iron.[25] While virtually all of the iron complexed with DFX in the bloodstream is protein bound,[50] the results seen in patient 4 suggest that under some circumstances DFX too may "shuttle" iron to DFO for excretion in the urine. As in the aforementioned studies, this was not always the case. Patient 1 also showed evidence of synergy when given the combination of drugs but had only a minimal shift toward urinary excretion of iron. In the other four patients, only fecal excretion of iron increased, the smallest increase being seen in patient 2, the one who responded best to DFX alone.

While eliminating the need for chelation 2 or more days each week may sound attractive to many patients, this approach would allow non-transferrin-bound iron, a potentially toxic form of iron, to accumulate in the plasma when no chelator is present.[4,51,52] Non-transferrin-bound iron has been linked to uptake of iron into the heart.[4,53] To obviate such a situation, DFX could be taken daily, supplemented with DFO two or three times a week, preferably on alternate days to minimize injection-related side effects. As shown in Table 6, two of four patients not in balance on DFX alone would achieve balance with 2 days of DFO supplementation, the others with 3 days of supplementation. As the body iron load is reduced, DFO could be given less frequently. Should hepatic and/or cardiac iron not decrease appropriately, the regimen could be modified accordingly.

Various regimens combining DFP and DFO have been used.[27] The two drugs have been given on the same day (simultaneous therapy) and sequentially on different days (alternating therapy), the pattern of administration/days of usage differing widely. While the primary goal may have been directing chelation to the liver or heart, or to minimizing toxicity in the face of declining body iron burden, tailoring the regimen to the lifestyle of the patient may be just as important. A similar approach could be taken with the combined use of DFX and DFO. Maintaining some measure of daily chelation is undoubtedly the best approach. With values of liver and heart iron available, the physician and the patient should be able to agree upon an appropriate/flexible regimen to deal with the situation at hand. Finally, in the long run, combining DFX and DFP, the two oral chelators, may prove to be the most versatile approach to chelation therapy. Preliminary studies are encouraging.[54,55]

Table 6. Iron balance (%) related to the frequency of combination therapy.

Regimen	COM 0 Days DFX 7 Days	COM 1 Days DFX 6 Days	COM 2 Days DFX 5 Days	COM 3 Days DFX 4 Days	COM 4 Days DFX 3 Days
Patient 1	61	89	116	143	170
Patient 2	129	149	169	188	208
Patient 3	45	68	91	114	137
Patient 4	29	59	89	120	150
Patient 5	66	95	124	153	183
Patient 6	102	125	149	173	196

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Authorship and Disclosures

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