Italian Society of Hematology practice guidelines for the management of iron overload in thalassemia major and related disorders

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ABSTRACT

New measures of iron accumulation in liver and heart (superconducting quantum inference device and magnetic resonance imaging), and oral iron chelators (deferiprone and deferasirox) are available for managing iron overload in thalassemia major. To assure appropriate use of these new health technologies, the Italian Society of Hematology appointed a panel of experts to produce clinical practice-guidelines for the management of iron overload in thalassemia major and related disorders. The analytical hierarchy process, a technique for multicriteria decision analysis, was applied to relevant key questions in order to identify the alternative strategies, generate explicit criteria for their evaluation, and check how well the alternatives fulfilled the criteria. The result of a comprehensive systematic review of articles released from 1990 to 2007 was used as a source of scientific evidence to compare the decisional options pairwise, and select the final recommendation. Every step in the model was developed from questionnaires and group discussion. The resulting recommendations advise about which examination to carry out in order to plan iron chelation therapy, when to start iron chelation, which iron chelator to choose in regularly transfused patients, how to monitor iron chelation therapy, and when and how to switch standard therapy.

Key words: clinical practice guidelines, systematic review, thalassemia major, sickle cell anemia, deferoxamine, deferiprone, deferasirox

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Introduction

Iron overload resulting from multiple red cell transfusions over a long period of time is a complication of thalassemia major and other thalassemia-like congenital anemias. Its detrimental effect can lead to organ compromise and, eventually, death. Managing iron overload in thalassemic syndromes requires a reliable assessment of excess iron load and organ iron distribution. Over the last years, non-invasive techniques such as superconducting quantum interference device (SQUID) and magnetic resonance imaging (MRI) have led to the conventional iron overload diagnostic methods, such as serum ferritin (SF) and liver iron concentration (LIC) by liver biopsy. Furthermore, strategies to improve deferoxamine (DFO) chelation regimens have led to the discovery and use of new and orally active iron chelators, deferiprone (DFP),[1,2] and deferasirox (DFX).[3]

These developments have heralded a new era for iron chelation, with the expectation of reducing organ iron burden, improving function and, ultimately, survival. However, integrating scientific evidence of the appropriateness of these new health technologies may lead to conflicting conclusions being made. These may in turn result in variations in clinical practice, with related disease costs and patient outcome.

In order to offer patients the most appropriate treatment, the Italian Society of Hematology commissioned a project to produce recommendations for the use of new diagnostic

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technologies and iron chelators in thalassemia major and related disorders. Thalassemia in Italy is still a major health problem, and Italian hematologists caring for patients with thalassemia are largely involved in the development and appraisal of new diagnostic techniques and in clinical research on the effectiveness of new chelators.[4–11] This has produced a group of acknowledged experts that have a comprehensive mastery of scientific and practical information that can give the most appropriate judgment.

Providing recommendations for management of iron overload in thalassemic syndromes today must involve decisions which are multifactorial in nature, and whose metrics are variable and difficult to define accurately. In an attempt to consider all the factors that may affect these decisions, analytical hierarchy process, a multiple-criteria decision-making technique,[12,13] was applied in this study. The final aim of the project was to support the clinical practice of hematologists, transfusionists and internists who care for patients with thalassemia major and related disorders.

Design and Methods

Organization

Two chairmen (*ST* and *GB*) appointed an expert panel of eight senior hematologists, selected for their expertise in research and clinical practice of thalassemia or other iron loading disorders, and an advisory committee chaired by two clinicians expert in clinical epidemiology (*GB* and *MM*) to support the systematic review of literature and to guarantee the methodology of the process.

Framing the domain of recommendations

During an initial meeting, the expert panel agreed on the aim of the project: to develop recommendations for the optimal treatment of iron overload in patients with thalassemia major. The expert panel agreed that the recommendations produced should be valid in the context of thalassemia major and related disorders, such as HbE/thalassemia, and sickle cell anemia.

The areas of major concern in the management of iron overload in thalassemia major and related disorders were selected by generating and rank-ordering clinical key-questions using the criterion of clinical relevance, i.e. impact on the management of patients and risk of inappropriateness, through iterative questionnaires (Delphi process).[14] The five candidate key-questions that ranked highest formed the set of questions of the present guidelines.

Literature inquiry and evidence analysis

The advisory committee performed MEDLINE, EMBASE and Cochrane Databases searches of English-language literature using pertinent Medical Subject Headings (MeSH) and terms. The electronic databases were initially searched in April 2006 (period covered: from January 1990 through March 2006), and the search was updated in April 2007. Additionally, the proceedings of the latest annual meetings were searched for relevant unpublished evidence. Investigators and pharmaceutical companies identified as being active in the field were asked to provide unpublished data or studies.

Two reviewers independently appraised and extracted details of selected articles that addressed the methods of measuring iron overload and the therapy of iron overload in thalassemia major, sickle cell anemia and congenital transfusion-dependent anemias using standardized extraction forms. For therapy studies, the following items were extracted: place of publication, study characteristics, population characteristics, detailed nature of intervention, comparator, concealment of allocation and outcomes. The study design was graded using the grading system elaborated by the Scottish Intercollegiate Guideline Network (SIGN), which grades at the top metanalyses and randomized clinical trials.[15] For studies evaluating tests, the following items were extracted: prospective or retrospective design, inclusion of consecutive patients, time when the test was carried out, number of patients, gender, age, duration of therapy. For studies evaluating the prognostic value of tests, validity of selected articles was assessed according to whether the study group was well-defined, the population representative, the criteria of patient selection defined, adequate follow-up, and outcome definition. No grade of methodological quality was given since no score received general agreement. Narrative synthesis methods were then used to integrate findings into descriptive summaries.

Framing the decision model

For each of the defined key-questions, we framed the decision process needed to arrive at the final recommendation as an analytical hierarchy process. For each of the key questions, a set of candidate alternative decisions was proposed by the expert panel in a Delphi process.[14] The appropriateness of candidate options was determined by comparing them according to criteria that were explicitly generated in order to make clear the expert's judgments regarding which considerations are pertinent and their relative importance. Using a bottom-up approach, comparison of the options was made according to their ability to fulfill one of the selected criteria. This part of the process took place in consensus meetings using the nominal group technique, i.e. a face to face ordered group discussion process.[16] Literature-derived evidence analysis was extensively used in this process to support the decision. If 80 percent or more of consensus about which of the two alternatives to select was reached, the selected alternative was subsequently submitted to pairwise comparisons with the next option of the group until every pair of options was evaluated. The final list of options formed the core of the recommendations. Recommendations on therapy were graded according to SIGN.[15]

Results

Measures of body iron load requiring initiation of iron chelation therapy

The expert panel concluded that, in general, in children regularly transfused and who have a well known transfusional history, the selected decision criteria for recommending iron tests were accuracy, safety, availability and cost of quantitative methods for measurement of small body iron load. The competing options included SF, LIC measured by biopsy, SQUID or MRI.

Since it was documented that LIC by biopsy and total body iron stores were highly correlated (R=0.98; p= ≤0.001),[17] liver biopsy was considered the gold standard for measurement of total body iron. Nine studies with more than 10 patients that analyzed the accuracy of SF were selected (Table 1).[4,9,18-24] Strong linear correlation (R^2=approximately 1.0), enabling precise quantitative estimation of body iron content, was demonstrated in one study[20] but only in patients without a histological picture of liver hepatitis. There was good linear correlation (R^2 >0.5) in four out of the remaining studies[17,18,23,25] but in one of them, only in patients with lower iron burden.[18] Quality limitation of the studies were sample size (only four studies had analyzed more than 100 patients), and directness (all of them analyzed a population of patients who had started iron chelation therapy and included patients with high iron burden).

Two studies that evaluated the accuracy of LIC by SQUID were selected.[7,25] Strong linear correlation (R^2 approximately 1.0) between LIC by biopsy and SQUID was demonstrated in one of them.[25] However, in the larger study group,[7] correlation was poor (R^2=0.21), and LIC by biopsy was generally greater than by SQUID. Nine studies of at least 10 thalassemic patients that evaluated the accuracy of measurement of LIC by MRI, and included a quantitative measurement of MRI signal and a detailed description of the patient population were selected (Table 2).[4,22,24,26-32] Strong linear correlations (R^2=approximately 1.0) were demonstrated in four studies.[4,27-29] The best result was obtained with the R2 methodology which resulted in a curvilinear relationship between R2 and LIC by biopsy over the entire clinically relevant range of LICs.[31] In two studies, the correlation between T2-T2* and LIC by biopsy was less close in patients with fibrotic livers than in those non-fibrotic.[4,28]

The expert panel concluded that, in general, the consistency of the results from studies aimed at meas-

Table 1. Studies reporting the correlation between serum ferritin evaluation and measurements of body iron content in thalassemia major and related disorders.

First author, year (reference)	*Patients studied*	*Number of patients with thalassemia major or related disorders*	*Method of body iron content measurement as standard*	*Body iron content*	*Iron chelation started*	*Corrected for viral hepatitis*	*R^2*
Letsky, 1974[18]	Thalassemia major	19	LIC by biopsy	NR	In all patients	NR	0.56
Worwood, 1980[19]	Thalassemia major	124 transfused	Number of units of blood received	198±110 units of blood	In some patients	No	Patients receiving <100 units of bood: 0.53 Patients receiving >100 units of blood: 0.01
Aldouri, 1987[20]	Thalassemia major	51	LIC by biopsy	0.6-6.5 mg Fe/g d.w.	Yes	Yes	0.92 for grades 1 and 2 hepatitis; 0.60 for grade 3 hepatitis
Mazza, 1995[21]	Thalassemia major	33	LIC by biopsy	1.6-31 mg Fe/g d.w.	Yes	No	0.36
Angelucci, 1995[4]	Thalassemia major	103	LIC by biopsy	From 32.5±14 μmol/g Fe/g d.w. (histological grade =absent) to 417±150 μmol/g Fe/g d.w. (histological grade = severe)	NR	No	0.10
Bonetti, 1996[22]	Thalassemia major	30	LIC by biopsy	1.1 to 27 mf Fe /g d.w.	Yes	NR	0.38
Telfer, 2000[23]	Thalassemia major	42	LIC by biopsy	NR	NR	NR	0.72
Voskaridou, 2004[24]	Thalassemia major and intermedia and sickle cell disease	80	LIC by biopsy	8.86±2.98 mg/g d.w.	All patients	NR	0.36 in thalassemia major; 0.65 in sickle cell disease
Cappellini, 2006[9]	Thalassemia major	NR	LIC by biopsy	<3 mg Fe/g dw >14 mg Fe/g dw	97.4%	NR	0.39

LIC: liver iron content; NR: not reported.

Table 2. Studies reporting the correlation between liver iron content by biopsy and by magnetic resonance imaging.

Reference	*Population*	*Number of patients with thalassemia major or related disorders*	*MRI index*	*LIC measured by biopsy (mg Fe/g d.w..)*	*R^2*
Gomori, 1991[26]	β-thalassemia	10	1/T2 and 1/T2*	3.18-8.95	0.86 for 1/T2 and 0.38 for 1/T2*
Papakonstantinou, 1995[27]	β-thalassemia	40	1/T2 and L/M	2.32-18	0.94 for 1/T2 and 0,59 for L/M
Bonetti, 1996[22]	β-thalassemia major	30	T2	1.1-27	0.67
Angelucci, 1997[4]	β-thalassemia	43	T2	NR	0.98 in patients without liver fibrosis or cirrhosis; 0.72 in patients with liver fibrosis or cirrhosis
Anderson, 2001[28]	β-thalassemia	27	T2*	NR	0.86 in patients without liver fibrosis or cirrhosis; 0.66 in patients with liver fibrosis or cirrhosis
Voskaridou, 2004[24]	β-thalassemia, sickle cell disease,	106	T2	8.86±2.98	0.67
Ooi, 2004[29]	β-talassemia patients	22	T1 and T2	7.23±3.68	0.58 for liver T1; 0.42 for liver T2
Wood, 2005[30]	Thalassemia major, thalassemia intermedia, aplastic anemia, hemochromatosis, heme-metabolism defect	99	R2	1.3-32.9	0.94
St Pierre, 2005[31]	Hereditary hemochromatosis, thalassemia major, βthal/Hb E	50	R2	0.3-42.7	0.96 (all patients)
Christoforidis, 2007[32]	Thalassemia major	26	T2	NR	0.754

uring the accuracy of SF was poor. However, reliable measurements could be obtained in patients with lower iron burden. Consistency of the results from studies measuring the accuracy of LIC by SQUID was poor and underestimation of LIC was a critical factor. MRI methods, at variance, were consistently correlated with LIC by biopsy. The precision of liver MRI measurement was dependent on the amount of iron in the liver, liver fibrosis, sequence and calibration factors. The expert panel agreed that there is no evidence that SQUID or MRI methods are more accurate than SF in measuring the limited amount of body iron in early transfused, non-chelated patients.

In patients whose transfusional history is not known and iron burden may not be predicted by the transfusional iron intake, the criterion the expert panel selected for deciding which measurement was necessary before starting a new chelation therapy was the accuracy in revealing the total iron burden in patients who may have severe iron overload. In this decision, safety, availability and cost of the measurement were considered of minor importance. Evidence analysis on the correlation between SF, SQUID and MRI imaging and LIC by biopsy was reconsidered in this setting (Tables 1 and 2). The panel concluded that SF is not sufficient to demonstrate high body iron content accurately.

Recommendations

Patients with thalassemia major or related disorders in the early transfusional period, and with a known transfusional history, need to have serum ferritin levels determined 1-2 months apart in order to have a baseline value of iron load to use for initiating iron chelation therapy.

Patients over 5 years of age and with an unknown previous transfusion history and/or inappropriate chelation therapy should have both serum ferritin and liver iron concentrations determined in order to plan iron chelation therapy.

Liver iron biopsy with iron measurement by atomic absorption spectroscopy remains the gold standard for the assessment of liver iron concentration. Evidence of the accuracy of non- invasive methods for assessment of liver iron concentration is sufficient to recommend MRI technology as a feasible alternative to liver biopsy. R2 sequences and individual local calibration are recommended. SQUID remains a method to be reserved for experimental use since there is no calibration homogeneity and liver iron concentration could be underestimated.

When to start iron chelation therapy

The panel identified as criterion for deciding the best time to start iron chelation that of avoiding a transfusional iron load that could produce end-organ damage. The literature revision was addressed to studies that compared the outcomes of chelation therapy which were started at different times.

There are no quantitative trials that prospectively

compared the outcomes of the disease according to the patients' age, transfusional load, or iron measurements at the start of chelation therapy. Four observational, retrospective outcome studies were analyzed.[33-37] The panel concluded that there is good evidence of the relevance of age and SF values as indicators for deciding to start chelation therapy. However, evidence of the optimal thresholds values of such parameters is lacking. The panel therefore made its decision according to the principles of good clinical practice.

Recommendation

The panel judged that in children who have been regularly transfused, iron chelation should be started after they have received more than 10 units of blood, or with serum ferritin levels of over 1000 ng/mL. In patients with an unknown previous transfusional history or inappropriate chelation therapy, iron chelation should be started when liver iron content is over the normal range of the method used.

First-line therapy in regularly transfused patients

The criteria for selecting the iron chelating agent for prophylactic use in regularly transfused patients were long-term efficacy and safety of the chelator along with the expected compliance with therapy. Selected studies should have a comparative design, include participants showing little evidence of iron overload without end-organ damage, and, in principle, the tested drugs should be given from the beginning of chelation therapy. Therefore, this review arbitrarily excluded studies in which, when comparing drugs, the mean or median value of SF was greater than 2,000 ng/mL or LIC by biopsy greater than 7 mg Fe/g dry weight (d.w.). An additional exclusion criterion was an excessive hepatic or cardiac iron load as the reason for starting the comparative iron chelation.

Eight studies which compared DFP to DFO were selected[10,32,37-43] (Table 3). Some of them did not meet the inclusion criterion of SF lower than 2,000 ng/mL. However, all of them met the criterion of LIC lower than 7 mg Fe/g d.w. No study included patients at the beginning of chelation therapy. Altogether, 231 evaluable patients received DFP or DFP plus DFO and 266 received DFO alone.

No study evaluated mortality as an outcome. Five trials evaluated cardiac function:[38-42] in three of them there was no significant difference in the mean improvement in left ventriculum ejection fraction,[38] ventriculi shortening fraction,[39] or left ventricular mass index between the two groups.[40] In two studies,[41,42] there was a significant difference between treatment groups with respect to changes in left ventricular ejection fraction. Six studies evaluated the change in LIC from baseline to the end of the trial.[10,32,37,38,41,42] In two of them, mean LIC reduction was greater in the DFP or DFP plus DFO treated participants than in those receiving DFO alone.[38,42] However, different levels of LIC at baseline, and the use of different techniques to assess LIC among the trials reduced the consistency of the results. Assessment of myocardial iron load reduction was a measure of efficacy in six trials.[32,38-42] In five of them,[31,39–42] the increase in MRI T2* (therefore reduction in myocardial iron content) was greater in DFP or DFP combined with DFO, than in DFO-treated patients. Mean change in SF from baseline to end of the trial was available in six studies,[10,32,39,41,42] showing that the difference was not statistically significant in five, while the between-group difference was significant in favor of the combined treatment group in one trial.[42]

Compliance was significantly better in the DFP group than that in the DFO-treated group in one trial,[37] but was similar in two other trials.[10,32] The ability to compare data on compliance was limited by the different measurement methods used. Safety was an end-point of all but three trials.[32,39,40] Safety review documented that 7 out of 167 (4.19%) patients treated with DFO interrupted the treatment because of side effects compared with 10 out of 155 (6.45%) treated with DFP or combined therapy. Neutropenia was reported in 1 out of 167 patients treated with DFO (0.59%) and 4 out of 152 with DFP or combined therapy (2.6%). Neither difference was statistically significant. One agranulocytosis was reported in DFP treated patients.[37]

Two randomized controlled studies comparing DFX to DFO and reporting separate results among patients with low iron burden were selected in this section.[9,43] LIC modification was the main endpoint of the studies. In one study of thalassemic patients,[9] those entering the trial with a LIC less than 7 mg Fe/g d.w., therefore taking low doses of DFX (5-10 mg/kg/d), resulted in an increase in LIC and SF in both arms. In the other study of sickle cell disease,[43] patients entering the trial with a LIC less than 7 mg Fe/g d.w., showed a statistically significant reduction of LIC only with DFX in the dose cohort of 10 mg/kg/d. No significant changes in SF were observed. Adverse events resulted in drug discontinuation in 5.3% of patients on DFX and 3.2% of patients on DFO, but the difference was not statistically significant. Compliance was measured as an endpoint in sickle cell disease patients,[43] indicating a high adherence to both treatment regimens. Satisfaction with treatment was separately reported in thalassemic patients.[44] All patients receiving DFX were satisfied with treatment and found it to be more convenient than DFO.

The panel agreed that the evidence on the efficacy of DFP or DFX oral chelators with respect to DFO standard therapy in the prophylaxis of iron overload was limited by the short-term evaluation. There is no strong evidence that DFP alone or in combination with DFO is superior to DFO alone in removing iron from the body, as measured by SF or from the liver. Evidence that DFP is superior to DFO alone in preventing iron accumulation in the heart came from studies whose efficacy measurement was directed towards the removal of small amounts of iron from the heart and not towards the prophylactic use of therapy. Evidence points to ineffectiveness of DFX in removing iron from the liver when compared with DFO in patients with limited iron overload when used at the tested doses. Evidence in sickle cell anemia,

Table 3. Studies included in the systematic review of iron chelators in patients with mild iron overload.

	Study arms	Drug dosage	Design	N. of patienst evaluated			Age of participants yrs.(mean)	Allocation concealment	Iron measures at baseline		Observation time	Outcomes measured
				Thalassemia major	Sickle cell disease	Other			Serum ferritin (μg/L), mean ±SD	Liver iron concentration (mg/g d.w.), mean±SD		
Olivieri 1997[37]	DFO/DFP	DFO=36.7±2.8 mg/kg night DFP=NR	RCT	DFO=18 DFP=19	0	0	NR	No	NR*	DFO= 6.9±0.9 DFP= 8.9±1.2	max 2 yrs.	LIC by SQUID; compliance with treatment
Maggio 2002[38]	DFO/DFP	DFO=50 mg/kg during 12 h for 5 days/week DFP=75 mg/kg in three daily doses	Parallel RCT	DFO=73 DFP=71	0	0	DFO= 21±4.2 DFO= 20±5.3	No	DFO= 2019±678 DFP= 2283±754	DFO=3.36 ±5.4 DFP=3.5±2.9	1 yr.	SF; LIC by biopsy; LIC and heart iron content by MRI; heart function;
Anderson 2002[39]	DFO/ DFP	DFO=37.4 mg/kg on 5.1 days per week via 24 hours subcutaneous or overnight infusion; DFP=80.5 mg/kg divided into three doses per day	Matched case-control study	DFO=30 DFP=15	0	0	DFO=29.4±7.1 DFP=29.0±6.3	No	DFO=1250±508 DFP=1236±651	ND	> 3 yrs.	SF; myocardial T2*; liver T2*; left ventricular mesurements
Pepe, 2006[40]	DFO/ DFP	DFO= 50 mg/kg via subcutaneous administration on 5 days/wk DFP=75 mg/kg into 3 doses/day	Matched case-control study	DFO=18 DFP=18	0	0	DFO=31±5 DFP=29±10	No	DFO=631±486 DFP=1174±911	ND	3.7 years	Liver T2*; global heart T2*; right ventricular EF%
Pennel, 2006[41]	DFO/ DFP	DFO=50 mg/kg/day for at least 5 days per week; DFP=75 mg/kg/day	Parallel RCT	DFO=32 DFP=29	0	0	DFO=26.2±4.7 DFP=25.1±3.8	Yes	DFO=2795±2441 DFP=1791±1029	DFO=6.32±5.8 DFP=6.16±6.0	1 year	SF; LIC;T2* heart, cardiac function and volumes
Galanello 2006[10]	DFO/ DFO alternated to DFP (DEP5 days a week, DFO other 2 day)	DFO alone= 37.8±8.9 mg/kg/day Alternating therapy: DFO 33.3±6.64 mg/kg,	RCT	DFO=30 DFO alternated to DFP=29	0	0	DFO 6.1 alone=19.8±6.1 DFP alternated to DFO=18.7±4.8	No	DFO=2257±748 DFP=2048±685	DFO=1.6±0.6 DFO alternated to DFP=1.6±0.7	1 year	SF, LIC by SQUID
Christoforidis, 2007[32]	DFO/ DFO plus DFP	DFO=30-50 mg/kg 5-6 times per week Combined therapy=DFO: 30-50 mg/kg 3-4 times per week, DFP: 75mg/kg/day	Observational prospective	DFO =32 DFO+DFP=16	0	0	14.7±3.7	No	DFO =1938 DFO+DFP= 2303	NR	4 yrs.	SF; liver MRI; myocardial MRI
Tanner, 2007[42]	DFO plus DFP/DFO plus placebo	DFO=40 to 50 mg/kg for a minimum of 5 nights per week DFP=75 mg/kg	Randomized placebo controlled, double blind trial	DFO=33; DFP+DFO=32	0	0	DFO=28.7±5.3 DFO+DFP=28.8±4.2	Yes	DFO=1574 (11%) DFO+DFP=1379 (11%)**	Liver T2*, ms>19: DFO=4.2 (0.52); DFP+DFO=4.9 (0.62)***	1 yr.	SF, Liver T2*, myocardial T2*, LV volumes and function
Cappellini, 2006[9]	DFO/ DFX	DFO=from 20 to 35 mg/kg; DFX=5-10 mg/kg	Randomized controlled phase III study (subgroup analysis)	DFO (LIC<7 mg/g dw)=93 DFX (LIC<7 mg/gdw)=93	0	0	DFO=17.3±9.96 DFX=17±9.47	No	NR	LIC<7 mg/g dw	1 yr.	SF; LIC by biopsy; net body iron balance
Wishinski, 2006[43]	DFO/ DFX	DFO=20-30 mg/kg; DFX=5-10 mg/kg;	Randomized phase II trial (subgroup analysis)	0	DFO (LIC<7 mg/g dw)=27 DFX (LIC<7 mg/g dw) =68	0	NR	No	DFO=2834 DFX=3460	<7	1 yr.	SF, LIC by SQUID, compliance with treatment

*DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; SF: serum ferritin; LIC: liver iron content; MRI: magnetic resonance imaging; RCT: randomized controlled trial; EF: ejection fraction; SQUID: superconducting quantum intereference device; ND: not determined; NR: not reported. **Serum ferritin was reported as geometric mean and coefficient of variation *** Liver T2* was reported as millisecond (geometric mean and coefficient of variation).*

however, pointed to better iron removal from the liver in patients with at least 3 mg Fe/g d.w. and with doses of at least 10 mg/kg. For all these reasons, existing evidence was judged insufficient to support the prophylactic use of new oral chelators in transfusional iron overload of thalassemia major or related disorders.

Recommendation

Children who start iron chelation therapy before 6 years of age, when the body iron burden is always modest, and in whom the goal of chelation therapy is the prophylactic maintenance of iron balance, should receive iron chelation with deferoxamine (level D). The better compliance of oral compounds make these new drugs attractive. The option of oral chelators in first line therapy should, for the moment, be considered investigational and should only be performed within clinical trials or registries.

Monitoring iron chelation

Monitoring patients during chelation therapy is aimed at avoiding both excessive iron deposition and excessive iron depletion, and allows the efficacy of therapy and the compliance to the chelator to be evaluated. The criterion the panel selected to use for deciding which is the best measurement for monitoring iron load during iron chelation therapy was the prognostic value of the test.

Studies including any sort of analysis of prognostic factors were selected. The prognostic value of SF was evaluated in six retrospective studies.[33-36,45,46] Hypogonadism, short stature, cardiac disease-free survival and death were the measured outcomes. For all the studies, study groups were judged well-defined, and the number of patients and the follow-up sufficient. However, the studies were judged to be limited by their different thresholds for SF value, and lack of a common definition of cardiac outcomes. The prognostic value of LIC by biopsy was evaluated in one retrospective analytical study[45] in which cardiac disease-free survival was significantly associated with initial LIC.

Monitoring cardiac function was shown to have prognostic value on symptomatic cardiac disease and death in three retrospective analytical studies,[35,47,48] while in another study it was not.[49] The validity of the studies was judged to be good for the number of patients and for the follow-up, but poor for the definition of cardiac outcomes. Two retrospective studies evaluated the prognostic value of measures able to monitor myocardial iron loading,[50,51] reporting that subjects with a low myocardial T2* were at risk of symptomatic heart failure and ventricular arrhythmias.

Recommendations

Patients undergoing iron chelation should receive periodic monitoring of serum ferritin. With a trend of increasing serum ferritin or decreasing serum ferritin below 1,000 ng/mL, liver iron content should be assessed in order to avoid under- or over-treatment.

Patients who have received determination of liver iron content before starting chelation therapy should repeat liver iron content every year during chelation therapy.

In patients with a poor chelation history or in which liver iron content documents non-optimal chelation therapy, T2 MRI heart iron content should be monitored every year.*

Switching to an alternative iron chelation therapy in patients uncompliant, intolerant, or refractory to DFO therapy

The criteria identified by the panel for switching to an alternative chelation therapy differed according to the clinical context. In patients with evidence of non-compliance to DFO or with severe adverse effects which preclude DFO continuation, but without evidence of severe iron overload, the panel decided that the criteria for selecting between alternative therapeutic approaches should be long-term efficacy, safety and compliance. The decision options were restricted between the two oral chelators DFP and DFX, and studies with a comparative design including patients showing little evidence of iron overload were analyzed (Table 3). No study directly compared the two oral iron chelators, therefore evidence for efficacy was taken indirectly from studies comparing the new oral chelators with DFO. Similarly, compliance and safety were first analyzed from these trials (as reported in the section on prophylactic chelation treatment). However, since safety was a highly influential criterion for the decision, the panel also considered studies without a comparative design but which evaluated the safety of oral iron chelators. Three cohort studies using the standard dose of 75 mg/day were analyzed for DFP including a total of 738 patients.[52-54] Post-marketing unpublished reports were taken into consideration for DFX (data on file kindly provided by Novartis). For DFP, the incidence of agranulocytosis and of severe neutropenia was of 0.5% and 4% respectively. There were reports of DFX recipients with hematologic disorders associated with marrow failure who developed neutropenia and thrombocytopenia, but the relationship between DFX with these events is uncertain. Long-term toxicity studies have now clarified that a serum creatinine increase from baseline is common during DFX therapy, but that this alteration never evolved into a true renal damage. Based on these safety considerations, the expert panel argued against the use of DFP as second-line therapy in patients without severe iron overload. For patients who develop severe iron overload during DFO therapy, the panel first provided a definition of how severe iron overload should be before a change in DFO iron chelation therapy is required. Since the panel identified SF, LIC and heart T2* MRI as monitoring procedures, the literature revision was addressed to studies that compared the prognosis of patients at different values of these tests.[33-36,45-49] Only non-prospective studies, with an uncontrolled or unblinded design, and in which the cut-off values of the test were determined without test performance analysis, were available. The panel reconciled the discrepant results according to principles of good practice.

The panel agreed that the major criterion for selecting the therapy in patients who failed DFO standard

therapy were the short- and long-term efficacy of iron removal of the alternative strategy. Compliance and safety were not considered to be important since iron chelation in this setting is a life-saving intervention. Literature reports two different approaches to an alternative chelation therapy. The first modality is DFO dose intensification.[55] The second modality is changing DFO with DFP or DFX or adding DFP to DFO. These different modalities were the selected options the panel submitted for comparison in the decision model.

Analysis of evidence first considered studies with a comparative design including participants in which the comparative strategies were started after documentation of excessive iron burden, or end-organ damage due to previous chelation failure. No such studies included intensive DFO therapy. Eight studies comparing DFP to DFO were analyzed (Table 4).[5,8,56-61] Altogether, 563 evaluable patients received DFO and 370 DFP or DFP plus DFO. The maximum observation time was nine years.[8] Two studies evaluated survival as an outcome.[5,8] In the first, time-to-event analysis noted 52 cardiac events, including 10 deaths, in patients while on DFO and no events while on DFP.[8] In the other study,[5] none of the 54 patients treated with DFP died, while 4 out of the 75 patients treated with DFO died during the study period. Cardiac events were the outcome of two studies.[5,8] More cardiac events occurred while on DFO, and the analysis of cardiac disease free survival over the 5-year period was significantly more favorable in the DFP group.[8] LIC was measured at baseline and at the end of the trial in one study,[60] and SF in six,[8,57-61] There was no significant difference in pre- and post-study LIC between patients using combined therapy and patients using DFO alone.[61] Patients receiving DFP, or DFP with DFO, showed a reduction in SF over time greater than patients who received DFO alone in two trials.[57,58]

Three studies were analyzed for the comparison of DFX with DFO in severely iron loaded patients[9,11,43] (Table 4). Altogether, 335 patients received DFX and 256 received DFO. The maximum observation time was one year. One study[11] included patients with a SF lower than 2,000 ng/mL or LIC lower than 7 mg Fe/g d.w. at the start of experimental therapy. Therefore the evidence was judged to be poorly directed towards the clinical question. Over the study duration, mean SF levels remained stable in the DFX 20 mg/kg/day and DFO groups, whereas there was a tendency for SF values to decrease modestly over time in patients randomized to DFX 30 mg/kg/day. SQUID assessments performed at the end of study showed an average reduction in LIC similar to that of the DFX 20 mg/kg/day and DFO groups, when compared with the values obtained at baseline.[11]

Changes in cardiac T2* MRI and LVEF due to DFO or DFX were reported in abstract form.[62] In a total of 23 patients treated with DFX, myocardial T2* improved significantly, while there was no significant change in LVEF before or after treatment over the same period. Patients treated with DFO also showed a small non-significant increase in myocardial T2*.

The panel concluded that in patients with high iron burden due to DFO failure, there is evidence that DFP in combination with DFO is able to reduce body iron burden more than DFO at standard dose, and that DFP is able to remove iron from the heart and to reduce cardiac events, including mortality, over a long period more efficiently than DFO. Even though evidence was provided by studies with a non-prospective design, time and selection biases were appropriately analyzed and excluded. By contrast, the studies with DFX provided evidence that the amount of iron removal achieved from DFX at doses of 20-30 mg/kg does not differ from that with DFO at standard doses. Furthermore, evidence of the ability of DFX to remove iron from the heart is based on a small number of patients.[63] No study evaluated mortality as an outcome.

Even in the absence of direct and comparative evidence of the efficacy of intensive chelation therapy with DFO, the panel decided to provide recommendations on its use based on consensus statements.

Recommendations

For patients with evidence of non-compliance to deferoxamine, or with severe adverse effects from deferoxamine which preclude its use, but without existing or pending severe iron overload, an oral iron chelator should be used as an alternative to deferoxamine therapy (level D). The lack of studies comparing deferiprone with deferasirox in thalassemia major or related disorders did not allow the panel to recommend one of them on the basis of scientific evidence on long-term efficacy. The panel felt justified in recommending deferasirox as the alternative therapy to deferoxamine on the basis of its better safety profile compared with deferiprone (level D). Deferiprone should be considered in the case of resistance or intolerance to deferasirox (level D).

Patients who develop severe iron overload (serum ferritin higher than 3,000 ng/mL maintained for three months at least, liver iron content higher than 15 mg/g d.w., or heart T2 <12 msec) or overt iron-related cardiomyopathy (left ventricular ejection fraction <55%, arrhythmias, cardiac failure) should receive "intensive" or "combined" iron chelation therapy. The panel judged that the first choice for combined therapy is deferoxamine associated with deferiprone (level B).*

Patients who develop life-threatening cardiomyopathy should receive continuous intensive or combined chelation therapy.

Discussion

The recommendations issued in this report have been generated by a panel of experts to strike a balance between research results and practice. All evidence concerning the clinically relevant key questions on iron overload in thalassemia major or related disorders were collected and evaluated in both their single quality and in their overall consistency using the current methodology for systematic reviews. Experts of the field judged whether the body of evidence was sufficient to provide any recommendation in a deci-

Table 4. Studies included in the systematic review of iron chelators in patients with severe iron overload.

First author, year (reference)	Study arms	Target or actual doses of the drugs	Design	No of participants			Age of participants, years (mean ± SD)	Allocation concealed	Iron tests at trial commencement		Observation time	Outcomes measured
				Thalassemia major	Sickle cell anemia	Other			SF	LIC		
Olivieri, 1990[56]	DFO/DFP	DFO=50 mg/kg daily DFP=50 mg/kg daily	Cross-over trial	24	0	2	23±8	No	2463±1746	ND	4 days each arm	Urinary iron excretion
Taher, 2001[57]	DFO/DFP	DFO=25-50 mg/kg/d at least 5 days a week DFP=75 mg/kg in 3 divided doses	Comparative non-randomized trial	DFO=40 DFP=15	18 (DFP)	1 (DFP)	DFO=17±4 DFP= 20±1	No	DFO=3480±417 DFP=3663±566	ND	2 yrs.	SF; compliance with treatment
Mourad, 2003[58]	DFO/DFO plus DFP	DFO=40-50 mg/kg/day by subcutaneous infusion on 5 to 7 nights each week; DFP=75 mg/kg in 3 divided oral doses	Parallel RCT	DFO=14 DFO plus DFP=1	0	0	12-40	No	DFO= 5506±635 DFP plus DFO=4153 ±517	ND	1 yr.	SF; urinary iron excretion
Piga, 2003[5]	DFO/DFP	DFO=20 to 50 mg/kg/day, 8-12-hour subcutaneous infusion, 4-7 days a week DFP= 25-100 mg/kg/day divided in 3 doses	Retrospective observational study	DFO=75 DFP=54;	0	0	DFO=19.4 ± 6.9 DFP=17.1± 4.1	No	DFO=1809± 1464 DFP=2033± 919	ND	At least 4 yrs.	SF, cardiac disease, overall survival
Gomber, 2004[59]	DFO/DFP/ DFO plus DFP	DFO = 40 mg/kg/day over 8-10 hours, 5 days a week DFP=75 mg/kg/day in 2-3 divided doses DFP+DFO= 75mg/kg/day in 2-3 divided doses daily and DFO 40 mg/kg/day over a period of 8-10 hours 2 days a week	3-arm parallel RCT	DFO=7 DFP =9 DFP+DFO = 10	0	0	Children	No	DFO=5077±1714 DFP=2672±886 DFO+DFP=3347 ±1526	ND	6 months	SF, urinary iron excretion
Borgna-Pignatti, 2006[8]	DFO/DFP	DFO=30-50 mg/kg per day, 5 to 6 times a week DFP=75 mg /kg daily in 3 divided doses	Observational	DFO= 359 DFP=157	0	0	DFO=17.4 (1.58-25.1) DFP=17.5 (2.45-24.9)	No	DFO=1460 (160-9418) DFP=1870 (532-10632)	NR	9 years (0.02-8.9 yrs.)	SF; cardiac events; overall survival
Peng , 2006[60]	DFO/DFP/DFO combined to DFP (DFO administered 2-6 days each week;DFP every day)	DFO=30-50 mg/kg per day, 3-7 days per week DFP=75-80 mg /kg daily in 3 divided doses	Observational	DFO=26 DFP alone or in combination=88	0	0	DFO= 15±6.5 DFP alone=16.4±6.0 to 18.0± 3.8 DFO+DFP=17.6±5.6	No	DFO=2115±1830 DFP alone=2754± 891 to 4654± 5502 DFO+DFP=4699± 3340	NR	DFP= 27.7+-7.7 to 66.9 +-2.0	SF
Ha, 2006[61§]	DFO/DFO plus DFP	DFO=30-60 mg/kg/day for at least 8 hours per day, 2 days per week; DFP=75 mg/kg/day in 3 divided doses	RCT	DFO=16 DFO + DFP=20	0	0	20[§§]	No	NR	>7	18 months	SF, LIC by biopsy; compliance with treatment
Piga, 2006[11]	DFO/DFX	DFO=40 mg/kg given on 5 consecutive days each week DFX: 10 or 20 mg/kg	Randomized controlled phase II trial	DFO =23 DFX=48	0	0	DFO=22.7 (range 18-29) DFX=23.7 (range 17-33 for 10 mg/kg, and 25.6 (range 19.50) for 20 mg/kg		2000-8000	5-15	48 weeks	SF; LIC by SQUID
Vichinsky, 2006[43§§§]	DFO/DFX	DFO=20-60 mg/kg based on initial LIC; DFX=10 mg/kg or 10-30 mg/kg according to baseline LIC	Randomized open label phase II trial	0	DFO (LIC>7 mg/gdw)=36 DFX (LIC >7 mgFE/gdw)=64	0	DFO=16 (3-51) DFX=15 (3-54)	No	DFO=2834 (1015-15578) DFX=3460 (1082-12901)	>7	1 yr.	SF, LIC by SQUID; compliance to treatment
Cappellini, 2006[9§§§]	DFO/DFX	DFX=20-30 mg/kg DFO= from 35 mg / kg to >50 mg/kg (according to the LIC value)	Randomized controlled phase III study	DFO (LIC> 7 mg/g dw) =197 DFX (LIC>7 mg/g dw) =203	0	0	NR	No	NR	>7	1 yr.	SF; LIC by biopsy; net body iron balance

[§]The study included two populations of patients dividied according to liver iron content, thus it was analysed only for the poor chelated population. [§§]The study of Ha reported the median age of the whole population of patients divided in poorly –chelated and well-chelated. [§§§]Results on the subgroup component with higher iron liver burden (greater than 7 mg Fe/g w.t.) were analysed in this session.

sion process grounded on the concept that the relative benefit-to-risk balance of any decision results from a partially subjective process. As a consequence, consensus was a critical part of the present guideline production. The construct validity of the consensus methodology was assured by the analytical hierarchy multiple criteria decision-making process,[12,13] by which the complex problems were reduced into small, easily manageable parts, ensuring that all important considerations were made, and multiple viewpoints were integrated into the decision-making process in an explicit and unbiased manner.

The results of this project cannot be compared with others obtained with similar evidence- and consensus-based methodology. The systematic reviews of literature and guidelines on iron chelators produced over recent years are now out of date.[63-66] By using SIGN grading system for therapeutic recommendations, no level A sentence was issued in our document. A B level was attributed to the recommendation on using combined therapy with DFO and DFP in patients who develop severe iron overload or overt iron-related cardiomyopathy. Most of the recommendations were made by the consensus of the experts (level D), testifying for the absence of sufficient scientific evidence. Indeed, most of the trials considered in the systematic review had design, directness and concealment failures. This also applies to the most critical decision on the choice of first-line, prophylactic iron chelation in patients who start therapy or who switch standard therapy. Even though on November 2005 the FDA granted DFX accelerated approval for the treatment of chronic iron overload due to blood transfusions in patients over two years of age, and similar approval was granted by the EMEA in Europe in 2007, the present guidelines do not recommend DFX to be used instead of DFO in first-line therapy. The panel judged that the evidence on long-term efficacy and safety of DFX was not sufficient to allow approval of its use as first-line therapy in practice. The use of the drug in registries or clinical trials seemed a more cautious recommendation.

The treatment policy of these guidelines is provisional. An early update of the present guidelines in accordance with incoming evidence-based information should be expected and encouraged.

Authorship and Disclosures

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