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Longitudinal follow-up of patients with thalassaemia intermedia who started transfusion therapy in adulthood: a cohort study

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Summary

We longitudinally evaluated the effects of regular blood transfusions (BTs), in the real-life context of the Myocardial Iron Overload in Thalassaemia network, in patients with thalassaemia intermedia (TI). We considered 88 patients with TI (52 females) who started regular BTs after the age of 18 years. Magnetic resonance imaging was used to quantify iron overload and biventricular function. For 56·8% of the patients there were more than two indications for the transition to regular BTs, with anaemia present in 94·0% of the cases. A significant decrease in nucleated red blood cells, platelets, lactate dehydrogenase, bilirubin, and uric acid levels was detected 6 months after starting regular BTs. After the transition to the regular BT regimen there was a significant increase only in the frequency of hypothyroidism and osteopenia, and a significant decrease in liver iron and cardiac index. The percentage of chelated patients increased significantly after starting regular BTs. The decision to regularly transfuse patients with TI may represent a way to prevent or slow down the natural progression of the disease, despite the more complex initial management.

Keywords: thalassaemia, blood transfusions, iron overload, complications.

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Based on the current definition, patients with thalassaemia intermedia (TI), also called non-transfusion-dependent thalassaemia (NTDT), do not require regular red blood cells transfusions for survival, at least during the first few years of life, but may require occasional blood transfusions (BTs) in some instances such as pregnancy, infection or growth failure.[1] Instead, the clinical features of patients with TI are the consequence of the long-term effects of anaemia, haemolysis, tissue hypoxia, and their compensatory response such as enhanced erythropoiesis and increased iron absorption.[2] The permanent effect of these pathogenetic events may cause clinical problems depending both on age and on the severity of the disease. On the other hand, more than a few observational studies have indicated a favourable impact of regular BTs on several morbidities of patients with TI.[3,4] Thus, in clinical practise adult patients with TI either for the prevention or for the management of complications such as decline in anaemia, extramedullary haematopoiesis (EMH), pulmonary hypertension (PHT), thrombotic events, cardiomyopathy, and fatigue are permitted to receive regular BTs, as suggested by current guidelines on NTDT.[5] However, clinical trials fully evaluating the balance of starting regular BTs in patients with TI are needed. In fact, well-known complications such as iron overload, transfusion-transmitted viral infection, and allo/autoimmunisation are the deterrents of this treatment and, currently, the decision and the timing of when to place patients with TI on regular BTs need to be more clearly defined.

To this purpose, in the present study we longitudinally evaluated the overall effect of regular BTs in the real-life and extensive context of the Myocardial Iron Overload in Thalassaemia (MIOT) Network, where most of the biochemical variables and morbidities typical of the patients with TI could be analysed and compared chronologically.[6] Furthermore, in a subgroup of patients who were started on regular BTs after 2006, we performed basal and follow-up magnetic resonance imaging (MRI) scans, where we quantified the short-term effects of this procedure on cardiac and hepatic iron, and biventricular function variables.

Patients and methods

Study population

Among the 402 patients with TI enrolled in the MIOT project, we retrospectively selected 88 patients (52 females) who started regular BTs after the age of 18 years. Patients were considered on regular BTs (i.e. transfusion-dependent TI) if they received at least four BTs per year.

The MIOT project was an Italian network comprised of 68 thalassaemia and nine validated MRI centres linked by a web-based network, configured to collect and share patients' data.[6] By protocol, patients have undergone an MRI scan every 18 ± 3 months since 2006. Clinical data were recorded from birth and updated at every MRI. Clinical follow-up continued until September 2018. Each haematologist completed a case-report form in order to update the clinical history between the last MRI and September 2018. The required minimum completion percentage was 60%.

The study complied with the Declaration of Helsinki. All patients gave written informed consent to the protocol. The Institutional Review Board approved this study.

Haematological and biochemical variables assessment

Blood was collected by venipuncture, allowed to clot, and then centrifuged to obtain serum samples. All haematological and biochemical variables were determined by commercially available kits.

Haematological and biochemical variables, assessed at 6 months before and 6 months after starting regular BTs, were taken into account.

Diagnostic criteria

The diagnosis of EMH was made by computed tomography (CT) or MRI. Endocrine complications were identified by the following criteria:

Diabetes mellitus (DM): fasting plasma glucose ≥126 mg/l or 2-h plasma glucose ≥200 mg/l during an oral glucose tolerance test or in a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose ≥200 mg/l.[7]

Hypogonadism: no spontaneous puberty or failure to proceed through puberty after the age of 16 years; after puberty, in females' menopause before the age of 40 years[8] and in males reduced libido, erectile dysfunction, low levels of gonadotrophin, free and total testosterone.

Hypothyroidism: high serum thyrotrophin concentration and normal or reduced free thyroxine levels (primary form), normal or low serum thyrotrophin concentration and reduced free thyroxine levels (central form).

Osteopenia was diagnosed in presence of a T-score measured using dual X-ray absorptiometry between −1 and −2·5.[7]

PHT was diagnosed if the trans-tricuspidal velocity jet, assessed by Doppler echocardiography, was >3·2 m/s.[9]

Arrhythmias were diagnosed only if electrocardiogram (ECG) documented and requiring specific medication. Arrhythmias were classified according to the American Heart Association (AHA)/American College of Cardiology (ACC) Guidelines.[10]

MRI

MRI examinations were performed using conventional clinical 1.5-T scanners from three main vendors (GE Healthcare, Milwaukee, WI, USA; Philips, Best, the Netherlands; Siemens, Erlangen, Germany) equipped with eight-element phased-array receiver surface coils. Breath-holding in end-expiration and ECG-gating were used for signal reception.

The T2* technique was used for iron overload assessment. Its reproducibility and its transferability within the MIOT network had been previously demonstrated.[11] For the heart, a multislice multiecho T2* approach was used. Three parallel short-axis views (basal, medium and apical) of the left ventricle (LV) were obtained at nine echo times (TEs).[12-15] For the liver a single mid-transverse slice was acquired at nine TEs.[16] T2* images analysis was performed using a custom-written, previously validated software program (HIPPO MIOT).[15] The software provided the T2* value on each of 16 LV segments, according to the AHA/ACC standardised myocardial segmentation.[17] Global heart T2* value was obtained by averaging all segmental T2* values. The value of 20 ms was used as 'conservative' normal value for the global T2* value.[15] For the liver, the T2* value was calculated in a large region of interest (ROI) of standard dimension, chosen in a homogeneous area of parenchyma without blood vessels.[18] As recommended,[19] liver T2* values were converted into liver iron concentration (LIC) values using the calibration curve introduced by Wood *et al.*[20], with a LIC >3 mg/g dry weight indicating significant hepatic iron overload.[21]

For the quantification of biventricular function variables, steady-state free procession cine images were acquired during 8-s breath holds in sequential 8-mm short-axis slices (gap 0 mm) from the atrio-ventricular ring to the apex. Images were analysed in a standard way[22] using MASS software (Medis, Leiden, The Netherlands). The inter-centre variability for the quantification of cardiac function has been previously reported.[23]

Statistical analysis

All data were analysed using the Statistical Package for the Social Sciences (SPSS®), version 13.0 (SPSS Inc., IBM Corp., Armonk, NY, USA).

Continuous variables were described as mean ± standard deviation (SD). Categorical variables were expressed as frequencies and percentages.

The normality of distribution of the variables was assessed by using the Kolmogorov–Smirnov test.

Correlation analysis was performed using Pearson's test or Spearman's where appropriate.

For continuous variables the difference between the pre- and post-BTs values was analysed by Student's *t*-test for paired data or the Wilcoxon signed-rank test. For categorical variables, the paired comparison of pre- *versus* post-BTs was performed using the McNemar's test.

A two-tailed $P < 0{\cdot}05$ was considered statistically significant.

Results

Study population

Table I shows the demographic and clinical data of our patients.

The patients started regular BTs at a mean (SD, range) age of 37·59 (10·88, 18–66) years.

In all, 50 (56·8%) patients presented with at least two indications for the transition to regular BTs. Of them, 47 (94·0%) had anaemia in association with one or more of the following conditions: EMH, PHT, cardiomyopathy, hypercoaugulability/thrombosis, and leg ulcers. The remaining three patients had EMH in association to PHT or leg ulcers. While, 38 patients had one indication for the transition to regular BTs: 34 anaemia, three EMH, and one cardiomyopathy.

At 6 months after the beginning of regular BTs, the patients reached a mean (SD) pre-BT haemoglobin of 9·32 (0·93) g/l, close to the target haemoglobin of 9·58 (0·83) g/l. The mean (SD) blood consumption was 102·02 (74·08) ml/kg/year.

Changes in haematological and biochemical variables

Table II shows the haematological and biochemical variables 6 months before and 6 months after starting regular BTs. A

Table I. Demographic and clinical data.

Variable	Value
Number of patients	88
Age at end of follow-up, years, mean (SD)	50·28 (10·72)
Males/females, *n*	32/56
Age at diagnosis, months, mean (SD)	91·82 (98·68)
Genotype, *n/N* (%)	
HBB:c.92+6T>C/HBB:c.92+6T>C	22/67 (32·8)
HBB:c.118C>T/HBB:c.118C>T	6/67 (9·0)
HBB:c.92+6T>C/HBB:c.118C>T	5/67 (7·5)
HBB:c.-137C>G/HBB:c.118C>T	4/67 (6·0)
HBB:c.92+6T>C/HBB:c.92+1G>A	3/67 (4·5)
HBB:c.93-21G>A/HBB:c.93-21G>A	3/67 (4·5)
HBB:c.118C>T/HBB:c.93-21G>A	3/67 (5·5)
HBB:c.92+6T>C/HBB:c.93-21G>A	2/67 (3·0)
Others	19/67 (28·4)
Age at first BT, years, mean (SD)	17·56 (13·38)
Age of starting regular BTs, years, mean (SD)	37·59 (10·88)
Splenectomy, *n* (%)	76 (86·4)
Age of splenectomy, years, mean (SD)	20·20 (10·98)
Previous hydroxyurea therapy, *n/N* (%)	22/69 (31·9)
Hydroxyurea therapy during BT, *n/N* (%)	5/69 (7·2)

BT, blood transfusion; HBB, haemoglobin subunit beta.

significant decrease in the nucleated red blood cells, platelets, lactate dehydrogenase, bilirubin, and uric acid levels was detected.

Complications related to BT

Three patients (two splenectomised) had been alloimmunised before the start of regular BTs, due to occasional BTs. Seven patients developed alloimmunisation and one patient autoimmunisation after starting regular chronic BTs. All these patients were splenectomised. The case of autoimmune haemolytic anaemia was resolved following the use of steroid therapy and the patient re-started regular BTs. All alloimmunised patients continued to be regularly transfused if they had red blood cell compatibility and did not further develop alloantibodies against other antigens.

Hepatitis C virus (HCV) infection was acquired by two patients, but they had been started on regular BTs before (1978 and 1989, respectively) the development (in 1992) of nucleic acid amplification testing of blood donors for HCV and human immunodeficiency virus.

Frequency of complications

After the transition to the regular BT regimen, patients were followed-up for a mean (SD) of 12·76 (8·43) years [median (interquartile range) 11·5 (9·76) years]. A weak inverse correlation was detected between the follow-up duration and the age of starting regular transfusions ($R = -0{\cdot}319$; $P = 0{\cdot}002$) (Fig 1).

Table III shows the frequency of different complications for both the pre- and the post-BTs periods. Data about complications were not present for all patients.

After the start of the regular BT regimen a significant increase in the frequency of hypothyroidism and osteopenia was detected. Frequency of thrombosis (deep vein thrombosis, thrombophlebitis, portal vein thrombosis) decreased after the start of regular BTs, but statistical significance was not reached.

The history of arrhythmias was available for 83 patients. Six patients had arrhythmias, all supraventricular, before the start of regular BTs. After the start of regular BTs, 10 new occurrences of arrhythmias (nine supraventricular and one ventricular) were registered, leading to a significant increase in the frequency of arrhythmias.

A total of 14 patients underwent cholecystectomy before the start of the regular BTs and seven patients after the start of regular BTs. The mean (SD) age at cholecystectomy was 32·11 (14·51) years. Considering only the patients who never had a cholecystectomy, the frequency of cholelithiasis was comparable before and after the start of regular BTs.

Six patients had a tumour (three hepatocellular carcinoma, one breast cancer, one lung carcinoma, one vulvar cancer) after the start of regular BTs.

The frequency of patients with at least one complication before and after the start of regular BTs was, respectively, 85·7% and 97·1% ($P = 0{\cdot}008$).

Changes in chelation therapy

The percentage of chelated patients increased significantly after starting regular BTs (51·4% vs. 98·6%; $P < 0{\cdot}00001$).

Of the chelated patients before the start of regular BTs, 34·3% received deferoxamine (DFO), 5·7% deferiprone (DFP), 10% deferasirox (DFX), and 1·4% combined DFO + DFP. At the end-of-study, 58·6% of patients were treated with DFX, 20·0% with DFP, 12·9% with DFO, 5·7% with sequential DFX/DFP, and 1·4% with combined DFX + DFP.

Table II. Haematological and biochemical variables 6 months before and 6 months after starting regular BTs.

Variable	Number of patients	Before start of regular BTs, mean (SD)	After start of regular BTs, mean (SD)	*P*
Pre-transfusion haemoglobin, g/l	37	8·07 (0·94)	9·35 (0·89)	<0·0001
WBC, cells/mm^3	46	22 450·21 (36 630·04)	18 935·46 (20 126·20)	0·259
NRBC, %	31	112·15 (110·23)	76·81 (139·49)	0·002
Platelets, 10^3/mm^3	45	709·88 (611·31)	577·54 (252·06)	<0·0001
LDH, u/l	40	607·42 (300·57)	479·60 (235·83)	<0·0001
Direct bilirubin, mg/l	41	0·70 (0·51)	0·57 (0·32)	0·028
Indirect bilirubin, mg/l	38	2·35 (1·79)	1·79 (1·27)	0·001
Proteinuria, mg/l	42	40·85 (48·13)	36·93 (41·23)	0·694
Serum creatinine, mg/l	42	0·62 (0·23)	0·63 (0·18)	0·201
Uric acid, mg/l	37	5·13 (2·01)	4·60 (1·79)	0·014
AST, u/l	45	35·39 (27·19)	33·80 (25·76)	0·162
ALT, u/l	46	28·95 (26·93)	32·59 (31·22)	0·166
Serum ferritin, ng/ml	44	818·64 (853·17)	947·99 (890·09)	0·134

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; NRBC, nucleated red blood cells; WBC, white blood cells corrected for nucleated red blood cells.

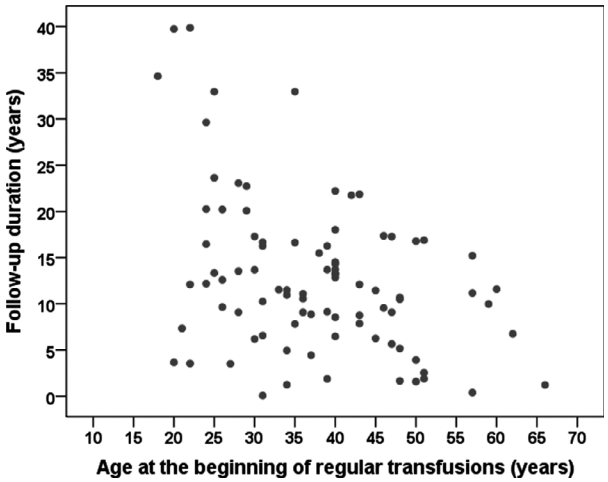

Fig 1. Scatter plot of follow-up duration *versus* age at the beginning of regular transfusion therapy.

Changes in MRI variables

In all, 16 patients had a MRI scan before and after starting regular BTs. All patients were scanned at least 3 months after starting BTs [mean (SD) time interval 1·08 (0·64) years].

Table IV shows the MRI variables at both scans (pre- and post-BTs).

There was no significant difference between the pre- and post-BTs global heart T2* values. All patients had normal pre-BTs global heart T2* values (≥20 ms), while one patient had a pathological post-BTs global heart T2* value (= 15·3 ms). This patient was not chelated at the first MRI and had started chelation therapy with DFX (20 mg/kg/day) 10 months before the second MRI. He showed severe hepatic iron overload at both scans (MRI LIC >14 mg/g dry weight).

A significant decrease in MRI LIC values was detected. Four patients (25%) had normal pre-BTs MRI LIC values and remained in the same status after starting regular BTs. All of them were chelated at both scans. Of the 12 patients (75%) with pre-BTs hepatic iron overload, four had no post-BTs hepatic iron overload and all were chelated at both the MRI scans. Eight patients had hepatic iron overload at both the scans: three patients were chelated at both scans, while the remaining five patients were chelated only for the post-BTs MRI.

Among the biventricular function variables, a significant decrease in the cardiac index was detected.

Discussion

Currently, the access to important procedures such as BTs and/or iron chelation has become more and more prevalent in Western countries. Life-expectancy has considerably increased among patients with thalassaemia major (TM), becoming comparable to that of patients with TI, as recently recognised in a large cohort of patients with thalassaemia from Italy.[24] Even if it has been clearly established that TI represents a wide spectrum of genetic entities without a clear distinction from TM, the decision to transfuse or not regularly transfuse patients with TI may be 'a dilemma'. In the absence of validated biomarker(s) predictive of the course of the disease[25], it mostly relies on physicians' expertise, particularly towards patients with milder forms, where the rationale is usually to prevent a possible forthcoming increase in disease clinical burden. The present study firstly analyses the practice of BT management among Italian patients with TI. Our present data firstly highlighted a conspicuous use of this practise, which involved approximately a fifth of the patients with TI enrolled in the MIOT network and reflected the

Table III. Comparison between the frequency of different complications in the pre- and post-BTs periods. The new occurrences and the remissions after the start of the regular BT regimen are indicated.

Complication	Number of patients	Comparison between pre- and post- regular transfusions			New occurrences after start regular BTs, *n*	Remissions after start regular BTs, *n*
		Before start of regular BTs, *n* (%)	After start of regular BTs, *n* (%)	*P*		
DM	81	3 (3·7)	4 (4·9)	1·000	2	1
Hypogonadism	80	7 (8·8)	12 (15·0)	0·063	5	0
Hypothyroidism	77	6 (7·8)	13 (16·9)	0·016	7	0
Osteopenia	67	33 (49·3)	49 (73·1)	<0·0001	18	2
EMH	72	20 (27·8)	20 (27·8)	1·000	3	3
Thrombosis	73	11 (15·1)	4 (5·5)	0·092	3	10
Ulcers	74	19 (25·7)	19 (25·7)	1·000	6	6
Pulmonary hypertension	64	7 (10·9)	10 (15·6)	0·375	4	1
Arrhythmias	83	6 (7·2)	16 (19·3)	0·002	10	0
Cholelithiasis in patients without cholecystectomy	51	20 (39·2)	18 (35·3)	0·774	5	7
Tumours	79	0 (0·0)	6 (7·6)	–	6	–

DM, diabetes mellitus; EMH, extramedullary haematopoiesis.

Table IV. MRI variables at the scans performed before and after the transition to regular BTs.

Variable, mean (SD)	Before start of regular BTs	After start of regular BTs	*P*
Global heart T2*, ms	38·59 (4·13)	37·82 (7·79)	0·642
MRI LIC, mg/g dw	10·91 (11·44)	6·15 (6·99)	0·020
Left atrial area, cm^2/m^2	13·57 (4·00)	13·03 (3·61)	0·612
Right atrial area, cm^2/m^2	12·65 (2·54)	12·69 (1·96)	0·959
LV EDVI, ml/m^2	100·96 (20·20)	92·57 (21·39)	0·097
LV ESVI, ml/m^2	38·33 (12·88)	33·93 (10·74)	0·115
LV SVI, ml/m^2	62·59 (9·54)	64·17 (19·72)	0·756
LV mass index, g/m^2	66·73 (15·02)	66·47 (16·44)	0·924
LV EF, %	62·47 (5·94)	63·13 (5·34)	0·673
LV cardiac index, $l/min/m^2$	4·46 (1·02)	4·25 (0·68)	0·442
RV EDVI, ml/m^2	91·03 (16·94)	86·71 (19·60)	0·212
RV ESVI, ml/m^2	31·24 (12·51)	30·43 (8·55)	0·697
RV SVI, ml/m^2	61·32 (9·65)	57·87 (12·62)	0·185
RV EF, %	67·07 (4·13)	64·68 (5·19)	0·060
Cardiac index, $l/min/m^2$	4·58 (0·76)	4·20 (0·80)	0·049

dw, dry weight; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; EF, ejection fraction; LIC, liver iron concentration; LV, left ventricular; MRI, magnetic resonance imaging; RV, right ventricular; SVI, stroke volume index.

management decisions performed over a long period of time (since MIOT establishment to September 2018), also preceding the year of publication of the NTDT guidelines.[5]

The genetic abnormalities of our patients were very heterogeneous (in high-risk populations), ranging from β0/β0 to β+/β+, in the absence of a predictive genotype. Interestingly, the mean threshold level of anaemia for initiating BT did not indicate a severe form of TI. It should be noted that 45% of the patients with TI had BTs because of more than one indication.

Most patients were started on BTs at pre-BT haemoglobin comparable to that recommended for TM. Interestingly, these patients had lower blood consumption with respect to patients with TM enrolled in the MIOT project [mean (SD) 102·02 (74·08) vs. 176·75 (51·91) ml/kg/year; $P < 0·0001$), thus suggesting the permanence of a residual higher erythropoietic drive. Following the start of BTs, we found not only the down-regulation of all erythropoietic and/or haemolysis indices,[26-28] but also a drop in platelets and white blood cell count, indicating a complex and pleiotropic effect on bone marrow function. On the other hand, renal function was not affected, likely because most patients had normal creatinine and were not hyperfiltrating at baseline.

The rate of erythrocyte allo- and autoimmunisation amongst our patients did not appear to differ significantly from that previously reported and revisited recently.[29] Usually TM has a higher endocrine involvement than TI. In the Optimal Care study, a large series of patients with TI were evaluated; in this study where only 21% of patients were aged >35 years, a prevalence of 1·7% DM, 5·7% hypothyroidism, and 17% hypogonadism was found and transfusional iron overload seemed to be the main factor in the occurrence of endocrinopathies.[30] Similarly, an increased risk of developing several complications, including endocrinopathies, has been reported in association with higher LIC values or serum ferritin levels.[31] A significant role for advancing age (even amongst paediatric and adult patients) in experiencing complications in TI has been also clearly demonstrated, particularly in untreated patients.[4] Considering the observation occurs over a long period of time, the increase in endocrinopathies seen in our present patients following the use of regular BTs appeared very modest, involving only hypothyroidism and osteopenia. Osteopenia shows a multifactorial pathogenesis and we found a high prevalence of osteopenia compared to that found (76%) in a younger Italian TI series, but mostly composed of patients who had never or only occasionally received a BT.[32] This finding likely reflects the valuable effects of the optimal chelation therapy practised in Italy, widely demonstrated in patients with TM.[33] On the other hand, age could possibly be the unique powerful factor in the onset of complications in our present series. It could be a factor when observing the paradoxical occurrence of new complications, such as leg ulcers or EMH, among those who were started on BT. However, it is also conceivable that in these cases, as already observed in a selected TM population for the occurrence of EMH,[34] there was an inadequate pre-BT haemoglobin level. Similarly, the occurrence of cancer and supraventicular arrythmias is a well-documented phenomenon associated with ageing in patients with thalassaemia.[33]

Anecdotally, in the period following regular BTs, many of the patients reported that they felt an improvement in their sense of well-being, despite being older in age. As well as the increase in haemoglobin, it is possible that the need for regular BTs necessitated the patient to spend more time in comprehensive care centres with an increased interaction with the staff, which could have also been involved in increasing their health-related quality of life.[5,35] However, we did not use a validated tool to evaluate the change in patient-perceived health impairment,[36] therefore, our present assessment was only a starting point for further and more detailed overall evaluation of quality of life.

Some more definite and precise observations come from the assessment performed in our present series, even though it involved a small number of cases. It was interesting to observe a paradoxical decrease in LIC following BTs, which obviously should be attributed to the almost complete use of the iron chelation therapy, but for which an overall lower morbidity is expected.[31] Similarly, despite transfusion iron, 94% of the patients still had a insignificant cardiac iron burden, confirming previous findings on the protective role of residual expanded erythropoietic/NTDT status.[34,37,38]

The idea that BTs may help to relieve most of the echocardiographic anomalies and the progression of

pulmonary hypertension and right heart failure is quite outdated,[39-41] and no prospective data are available using MRI. Our present data showed a decrease in biventricular end-diastolic volume indexes and cardiac indexes, but a significant difference between the pre- and post-BTs values was found only for the cardiac index, probably due to the low number of cases. These data seem to suggest a favourable impact of the BT regimen on cardiac haemodynamics, with potential positive effects against a high cardiac output state cardiomyopathy. Unfortunately, most MRI scans were performed only 1 year after the start of regular BTs and realistically more time is needed to counterbalance the effects of prolonged anaemia and to observe further improvement or even reversal of most pathological cardiac variables.

Overall, our present data showed that following the use of regular BTs and iron chelation therapy only a mild increase in most of the complications was recorded; we cannot exclude that it could be ascribable to ageing per se, as happens for general population.[42] Thanks to chelation therapy, the net iron balance seemed to be favourable amongst the assessable cases.

The lack of comparison both with a TI control population, where we can assess the natural advance in complications without the use of BTs, and with a similar transfusion-dependent TM population represents the main limitation of the present study. However, we believe that patients with transfusion-dependent TI, despite being chronically transfused, are different from those with TM and that this comparison would merit analysis and evaluation in a separate investigation. Other important limitations include the small number of patients and the lack of availability of some data with respect to the whole population. A multicentre study involving patients of other nationalities is recommended.

In conclusion, our present results suggest that in a country with a good national health system, the decision to regularly transfuse patients with NTDT may represent a way to prevent or slow down the natural progression of the disease despite the more complex initial management.

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Disclosures

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Author contributions

Paolo Ricchi conceived the study and wrote the paper. Antonella Meloni analysed the data and wrote the paper. Laura Pistoia and Vincenzo Positano were responsible for data collection. Anna Spasiano, Maria Rita Gamberini, Aurelio Maggio, Calogera Gerardi, Giuseppe Messina, Saveria Campisi, Massimo Allò, Stefania Renne, Riccardo Righi, Massimo Midiri, and Aldo Filosa collected the data. Alessia Pepe contributed to the interpretation of the results and wrote the paper. All authors contributed to critical revision and final approval of the version to be published.

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