C. R. Biologies 336 (2013) 164–172

Contents lists available at SciVerse ScienceDirect

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Medical sciences/Sciences médicales

Post-transfusional iron overload in the haemoglobinopathies

Surcharge en fer post-transfusionnelle dans les hémoglobinopathies

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ARTICLE INFO

Article history:
Available online 24 October 2012

Keywords:
Transfusion
Iron overload
Thalassemia
National registry
Sickle cell disease

ABSTRACT

In this report, we review the recent advances in evaluation and treatment of transfusional iron overload (IO). Results of the French thalassaemia registry are described. According to the disease, thalassaemia major or sickle cell anaemia, mechanisms and toxicity of iron overload, knowledge about IO long-term outcome and chelation treatment results, respective value of IO markers, differ. The recent tools evaluating organ specific IO and the diversification of iron chelator agents make possible to individualize chelation therapy in clinical practice. The severity of IO and the level of transfusional iron intake, the preferential localization of IO (heart/liver) as well as the tolerance and adherence profiles of the patient can now be taken into account. Introduction of cardiac magnetic resonance imaging for the quantification of myocardial iron and use of oral chelators have already been reported as decreasing the cardiac mortality rate related to IO in thalassaemia major patients. Long-term observation of patients under oral chelators will show if morbidity is also improving via a more continuous control of toxic iron and/or a better accessibility to cellular iron pools.

Mots clés :
Transfusion
Surcharge en fer
Thalassémie
Registre national
Drépanocytose

RÉSUMÉ

Nous rapportons les progrès majeurs réalisés dans le domaine de l'évaluation et du traitement de la surcharge en fer post-transfusionnelle au cours des dernières années, ainsi que les principaux résultats de la prise en charge des patients atteints de formes sévères de bêta-thalassémie résidant en France et répertoriés dans le registre national. La surcharge en fer consécutive aux transfusions régulières de concentrés globulaires concerne principalement deux maladies constitutionnelles de l'hémoglobine : la thalassémie et la drépanocytose. Concernant la surcharge en fer accompagnant ces deux hémoglobinopathies, elle diffère dans ses mécanismes, la fréquence de ses complications cliniques, le niveau de connaissance sur son pronostic à long terme, la documentation des bénéfices de son traitement et la pertinence de ses indicateurs paracliniques. Les nouveaux outils d'imagerie par résonance magnétique évaluant la surcharge en fer tissulaire et la diversification de l'arsenal thérapeutique avec l'utilisation des chélateurs du fer actifs par voie orale ont déjà permit une amélioration de l'espérance de vie des patients thalassémiques. Le traitement chélateur peut être individualisé car adapté à la localisation prédominante (cardiaque et/ou hépatique) et à la sévérité de la surcharge ainsi qu'au profil de tolérance et d'observance du patient.

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1631-0691/$ – see front matter
http://dx.doi.org/10.1016/j.crvi.2012.09.010

1. Introduction

Blood transfusions (TF) are lifesaving therapy for patients with thalassaemia and sickle cell disease (SCD). As each unit of transfused blood contains approximately 200 mg of iron without natural means of removing excess iron from the body, iron accumulates over years, excess iron from TF being initially distributed to macrophages and to the liver. IO gradually leads to damage of major organs such as the heart, the liver and endocrine organs. Chelation therapy allows the control of transfusion related IO with the aim to maintain both low iron stores and a correct iron balance. Chelating agents form a complex with iron, promoting its excretion by clearing plasma non-transferrin-bound iron and excess iron from cells, thus limiting exposure of tissues to toxic labile forms of iron. In the last years, two major advances have substantially changed the prognosis of transfusional IO in patients with thalassaemia major (TM): the diversification of chelator agents with the wide clinical use of oral drugs over the last decade, and the introduction of cardiac MRI to monitor cardiac iron. This review focuses on the recent data on the management of transfusional IO in thalassaemia and SCD and summarizes the main results of the French thalassaemia registry.

2. Iron overload in thalassaemia

Thalassaemia major is by definition a TF dependant anaemia where TF requirements are high, start in early childhood, and continue for life. Transfusional iron intake ranges from 0.3 to 0.6 mg/kg per day [1]. Thalassaemia is the disease where complications and therapy of IO have been particularly well investigated. Despite a continuous improvement of life expectancy [2,3], heart disease from transfusional IO remains the main cause of death. Iron overload is a progressive disease, reaching an advanced stage when symptoms arise. Tests are often available for a preclinical diagnosis permitting therapeutic intervention to prevent occurrence of overt symptoms: for instance glucose intolerance precedes diabetes and the mean elapsed time between the two stages has been calculated to be more than 3 years [4].

2.1. Iron overload monitoring in thalassaemia

Three primary parameters are used to assess the degree of IO and so the risk of developing IO complications: serum ferritin (SF) levels, liver iron concentration (LIC) and cardiac magnetic resonance imaging (MRI) T2* (Table 1). Each of these three parameters is an indicator for risk of iron induced cardiac toxicity and premature death: their serial use in clinical practice allows adjusting chelation therapy.

Table 1
Parameters used to assess the degree of IO and threshold values.

Threshold values	IO	Severe IO
SF values (ng/mL)	1000	2500
LIC (mg/gr dw)	3–7	15–20
Cardiac T2* (ms)	20	10

IO: iron overload; SF: serum ferritin; LIC: liver iron concentration.

2.1.1. Serial measurements of serum ferritin

Serial measurements of SF are an easy, convenient, worldwide available and cheap method to indirectly assess iron stores. Serum ferritin levels correlate well with total iron stores and statistically significant correlations between changes in LIC and SF have been found in TM patients [1]. Serial measurements of SF are, in clinical practice, the standard for identifying trends in iron status and for adapting chelation therapy every 3–6 months if necessary. SF levels above 1000 ng/mL indicate the start of chelation therapy and those of over 2500 the presence of severe IO requiring intensification of chelation. The aim of chelation therapy is to maintain SF levels below 1000 ng/mL, generally around 500. Lower SF thresholds have been used in clinical practice especially in TM adult patients and were safe and efficient [5].

2.1.2. Liver iron concentration (LIC)

Liver iron concentration (LIC) accurately reflects total body iron stores in thalassaemia patients [6], 70–80% of total iron amount being stored in the liver. LIC can be estimated with various methods: liver biopsy, magnetic biosusceptometry by the superconducting quantum interference device (SQUID) and magnetic resonance imaging. SQUID is a non-invasive and validated method but has limited availability, devices being available only in very few sites worldwide. MRI methods have been calibrated with LIC obtained from liver biopsies and assess LIC with the same accuracy than from a direct biopsy. As biopsy is an invasive procedure, LIC is nowadays most often evaluated with MRI. Several MRI approaches are possible, the relaxometry measurement of R2 being largely used in clinical practice. Examination is generally recommended every 1–2 years in patients with TM [7].

2.1.3. Cardiac MRI (measurement of cardiac T2*)

Over the last decade introduction of cardiac MRI (measurement of cardiac T2*), able to recognize preclinical cardiac iron deposition, has dramatically changed the management of IO. Iron shortens T2* relaxation time: cardiac T2* greater than 20 ms indicates normal cardiac iron content, values between 10 and 20 ms moderate IO, and less than 10 ms severe IO.T2* imaging has established the high prevalence of cardiac siderosis in adult TM patients treated with deferoxamine (approximately half of the adult patients with TM) and the correlation between low cardiac T2* values and impaired left ventricular ejection fraction (LVEF) [8,9]. Cardiac iron overloading occurs after 70–100 units of blood (14–20 g iron) in the absence of iron chelation and is rarely encountered in TM children under 10 receiving chelation therapy [10]. There is no correlation between cardiac iron and LIC in TM patients under chelation therapy. A severely shortened heart T2* predicts the occurrence of cardiac failure within 1 year from the detection. Cardiac T2* is the best marker for identifying patients at high-risk of heart failure and arrhythmia and its prediction value is superior to serum ferritin and liver iron measurements [11]. Reduction in

Table 2
Data from the French Thalassaemia Registry.

482 patients	TM	TM successfully transplanted	TM with graft failure	Thalassaemia intermedia
Number of patients	268	60	12	142
Median age (years)	21 (2–56)	15 (5–37)	28 (10–36)	28 (4–78)
Splenectomy (%)	54	20	58	48
TF: no/oc/reg	0/1/267	60/0/0	0/0/12	73/35/34
HCV % (nb RNA +)	20.6 (17/50)	10.4 (2/5)	25 (2/3)	9.5 (5/13)
Chelation therapy (%)	94	3.3	100	49
Median SF (ng/mL)	1104 (120–8553)	608 (98–4989)	954 (49–4989)	457 (13–6852)

TM: thalassaemia major; SF: serum ferritin; TF: blood transfusions.

cardiac deaths has already been reported in several cohorts or registries. For example, T2* CMR was introduced in the UK in 1999, and the death rate fell significantly in the TM UK registry from 2000 to 2003 [12]. This decrease was mainly driven by the reduction in the rate of deaths from IO with a 71% reduction in the annualized death rate from IO since 2000. Cardiac MRI is usually performed since the age of 8–10 years every 6–24 months, according to the presence and the severity of cardiac iron loading noted from the previous evaluation.

MRI can also be used to estimate pituitary gland and pancreas tissue IO [13,14]. Pituitary IO is correlated to liver and pancreatic iron but not to heart iron suggesting a fast and early pituitary iron loading. Pancreatic IO is a marker for future cardiac IO.

2.2. Results of the French thalassaemia registry

Thalassaemia is a very rare disease in France, and is predominant in patients originated from South Europe and North Africa. A national registry for beta-thalassaemia was set up in 2005 [15]. In October 2011, the French National Registry for beta-thalassaemia patients comprised 340 entries corresponding to patients with TM, with a median age of 21 (Table 2).

In this registry, the median serum ferritin (SF) levels, tested within the previous year was 1104 ng/mL for 95% of the TM patients under regular TF therapy. Sixteen percent of the patients had SF levels greater than 2500 ng/mL. The rates of IO related complications were 10%, 8%, 10% and 47% for cardiac failure, diabetes, hypothyroidism, and hypogonadism, respectively (Table 3). Parenthood was noted for 17% of the adult TM patients under regular TF and chelation, this finding illustrating the global improvement in the clinical care of TM patients. The frequency of organ damage related to iron overload increased with age with very rare occurrences of complications in childhood. SF levels did not differ according to the different age groups. We have analyzed the causes of death in TM patients living in France during the past ten years (2000–2010). Among 247 TM patients with a median age of 17 years in 2000, 23 deaths occurred. Fourteen deaths (61%) were of cardiac failure origin. Cardiac complications remain the leading cause of death. These results mirrored the delayed and progressive introduction of cardiac MRI in France: in 2011 only 58% of TM patients aged more than 10 years have been investigated with cardiac MRI. In the French registry mortality for non-transplanted TM patients between 2005 and 2011 was calculated at 6.6 for 1000 patient-years.

Table 3
Frequency of iron overload (IO) related complications in the French Thalassaemia Registry.

	Thalassaemia Major (%)	Thalassaemia intermedia (%)
Diabetes	21 (7.8)	4 (2.8)
Cardiac failure	28 (10.4)	6 (4.2)
Cardiac arythmia	22 (8.2)	6 (4.2)
Hypothyroidism	26 (9.6)	4 (2.8)
Hypogonadism (patients > 14 years)	88 (47)	20 (19)
Parenthood (patients ≥ 18 years)	27 (17)	40 (41)

3. Iron overload in sickle cell disease

The number of children with SCD receiving long-term transfusion therapy has significantly increased in recent years. In rich countries, mainly because of the primary prevention of stroke, around 15% of the paediatric SCD population is now receiving long-term TF treatment [16,17]. Due to the increasing life expectancy, an important proportion of adult patients with sickle chronic organ damage are under prolonged transfusion program to stabilize or improve organ dysfunction. Recently, a retrospective study conducted in a large SCD center in UK reported that the annual proportion of transfused adult patients has increased from 15% in 2000 to 19% in 2009 and the mean units transfused per patient from 11 to 21 [18]. The range of indications was wider over time as only half of the patients under planned chronic TF were currently treated for secondary stroke prevention.

3.1. Iron overload related complications in sickle cell disease

Iron extrahepatic distribution is typically less pronounced in sickle cell disease than in thalassaemia, and transfused SCD patients are less prone to IO related complications compared to TM patients. Long-term transfused SCD patients rarely demonstrated cardiac iron or cardiac failure [19]. No clear increase in the frequency of endocrinopathies was noted in patients with LIC of at least 10 mg/g dry weight or receiving a chronic TF program with an average serum ferritin level of at least 2000 ng/mL within the previous year when compared with non-transfused SCD patients [20]. Nonetheless iron related

liver disease appears to be a non-negligible cause of death in young adults and iron related cardiac failure may occur in iron overloaded SCD adult patients. Several non-controlled studies have underlined the relationship between IO and mortality in SCD adult patients. Mortality rate has been found significantly higher in the overloaded SS adult patients in a large retrospective study (64% versus 5%) [21]. Iron overload was also a leading circumstance of death in another study reporting autopsy findings [22]. More recently, the north America Multicenter Study of IO showed that transfused SCD patients had similar risk of death as those with TM with equivalent IO and TF history, cardiomyopathy being the cause of death in 5/17 SCD patients under chronic TF [20]. Nonetheless, liver seems the main organ targeted by iron toxicity in SCD. Association between liver cirrhosis and IO was documented by post-mortem study in SCD adults: cirrhosis was present in half of the patients who died with severe liver siderosis [22]. A retrospective review of 387 young adults followed between 1996–2006 during their first 10 years of transition from paediatric to adult care analyzed the causes of death for the 22 patients who died: 10 deaths were related to chronic IO, eight from liver failures and two from cardiac cause [23]. Several paediatric studies concerning SCD children under regular TF since 3.5–5 years without viral hepatitis found, despite high LIC (mean 10–15 mg/g dw), reassuring findings such as a low degree of liver fibrosis, mild liver injury, iron staining greater in Kuppfer cells than in hepatocytes [24–26]. On the other hand, changes in ALAT levels have been clearly associated with the degree of IO in the SCD paediatric population and longer follow-up under chronic TF are required to better evaluate related liver injury [27].

3.2. Mechanisms of iron overload in sickle cell disease

There are several possible explanations to the finding of less organ damage due to iron overload in SCD patients related to important differences in the mechanisms of iron overload between thalassaemia and sickle cell disease. There is no or relatively little ineffective erythropoiesis and thus no increased intestinal iron absorption in SCD. TF duration is generally shorter and TF rate lower than for TM patients, depending if transfusion are plain TF or manual exchange. For example, the average age at the start of TF therapy in STOP studies was 8.5 years and the average iron intake in CICL deferasirox controlled study was of 0.22 mg/kg versus 0.4 mg/kg per day for thalassaemia patients [1,28]. Patients with SCD are a heterogeneous population regarding TF modalities. Long-term erythrocytapheres therapy is not associated with transfusional IO: the use of automated exchanges effectively prevents IO and reduces iron load when associated with chelation use. Intermittent transfusions do not seem to produce significant iron overload in SCD patients but for patients receiving regular transfusion program SF values increase with the number of units of blood transfused. Finally, intravascular hemolysis and heme filtration also produce urinary iron loss. There are also differences in iron mediated toxicity and patterns of excess iron distribution between the two diseases. Due to inflammatory physiology of SCD, raised plasma hepcidine leads to a decreased iron release from macrophages and decreased transferrin saturation. Lower circulating non-transferrin bound iron (NTBI is rapidly taken up by hepatocytes and myocytes and is able to generate directly free radicals), lower percentages of transferrin saturation have been noted in SCD when compared to TM patients. So, subjects with SCD may be protected from iron related toxicity because of their chronic inflammatory state and preferential localization of iron in the reticuloendothelial system compared to parenchymal cells. Moreover, heme oxygenase is induced by intravascular hemolysis and ferritin synthesis stimulated.

3.3. Iron overload monitoring in sickle cell disease

The monitoring of IO is similar for SCD and TM patients and includes records of the amount of blood transfused, serial determinations of SF in the steady state, measurements of LIC. LIC is probably the best tool to evaluate body iron burden and chelators efficacy in SCD. Children receiving regular transfusion program in the STOP study (63% of patients receiving simple TF) experienced regular increase in SF values over time with the number of units of blood transfused [17]. SF levels were later more precisely analyzed in the prospective STOP studies [27]. Total iron load was calculated from the cumulative blood volume received before start of chelation therapy and in patients receiving only simple TFs. Averaged correlation between SF and TIL was $r = 0.7$. SF levels were well correlated with Total Iron Load (TIL) before the start of chelation therapy and when IO was mild. On the opposite range, when SF levels are high, greater than 2250 ng/mL, 85% of patients demonstrated LIC greater than 10 mg/g dw. Nonetheless in children with SCD on chronic TF serum ferritin level changes were nonlinear compared with increasing iron burden measured by LIC or TIL especially when SF between 1500 and 3000. Thus, in patients under TF and chelation therapy where SF levels are between 1500 and 2500, IO assessment should include LIC determination. LIC determination is also mandatory when calculation of TF iron load is not applicable: for patients under long-term regular TF and chelation therapy or patients receiving manual partial exchange, for patients who received intermittent TF over long period as intermittent transfusions do not always produce significant IO in SCD patients. Transfusion rate also influences markers of IO being more correlated to the number of TF per year than to the total number of received TF.

Young patients with SCA receiving chronic TF program during a mean time duration of 10 years have normal cardiac T2* and ejection fraction [19]. Nonetheless, a longer observation time is required to evaluate the exact frequency of cardiac involvement in the setting of transfused SCD patients.

3.4. Indications for iron chelation in sickle cell disease patients

The impact of chelation therapy on prognosis is clearly demonstrated in TM patients but less well documented in SCD. Registries are needed to better assess iron induced

morbidity/mortality and efficacy/safety of chelators in transfused SCD. Only one large randomized study is available, the CICL 109 study [28]. Nonetheless, despite the lack of strong evidence, most guidelines recommend initiating iron chelation therapy in patients starting chronic TF program who had received at least 20 TF (120 mL/kg) or with SF values consistently higher than 1000 ng/mL and for long-term transfused patients SCD patients when LIC greater than 7 mg/g dw (125 micromoles/g). So, indications are finally close to those established in TM patients. The aim of chelation is generally to maintain SF levels below 1000–1500 ng/mL.

4. Chelation therapy

Chelating agents form a complex with iron, promoting its excretion by clearing plasma NTBI and excess iron from cells and so limiting exposure of tissues to toxic labile forms of iron. Three chelators, deferoxamine, deferiprone and deferasirox are in clinical use and have been extensively studied. Two agents, deferoxamine and deferasirox, are approved for use as first line treatment of transfusional siderosis (second line in EU for DFX in cases of other anaemias than TM and patients with TM aged 2–5 years). The third chelator, deferiprone, is approved in TM patients since 1999/2004 in the EU when DFO is contraindicated or inadequate and since 2011 in US, when current chelation therapy is inadequate. Table 4 summarizes the main findings concerning the effectiveness and safety profiles of the three drugs currently licensed for the treatment of transfusional IO.

4.1. Deferoxamine (DFO)

DFO has been introduced in clinical practice in the 1970s. Its use has dramatically reduced morbidity and improved survival in patients with TM, heart disease remaining by far the most common cause of death [3,30]. DFO being administered parenterally via nightly/daily prolonged infusions (5–7 times a week), its efficacy is limited in a significant proportion of patients by poor adherence. Nonetheless, a small subset of patients currently prefers DFO or has returned to DFO after oral therapy failure. Incomplete prevention of cardiac iron localization has been established by T2* imaging: half of the adult patients under DFO treatment demonstrated the presence of cardiac iron. Concerning endocrines, 14% of adolescents still experienced a pubertal delay despite starting DFO early in life [2]. Deferoxamine is able when used as a continuous intravenous infusion to clear heart iron and reverse cardiac complications [29].

4.2. Deferiprone (DFP)

Deferiprone is an oral tablet given thrice daily. This small lipophilic molecule is more effective than DFO in removing cardiac iron, improving cardiac function (with significant amelioration in the mean LVEF of TM cohort

Table 4
Comparison of iron chelator properties.

	Deferoxamine	Deferiprone	Deferasirox
Plasma half-life/Route of administration	20–30 minutes/Parenteral subcutaneous or IV	2–3 h/Oral	8–16 h/Oral
Liver/Heart efficacy	+++/+	++/+++	+++/++
Advantages	Long-term safety record, 24 hour continuous administration for cardiac siderosis	Better cardiac outcome in epidemiologic and cardiac MR studies/DFO Increase in LVEF and small increase in LVEF is associated with improved survival Intensive chelation therapy when combined with DFO	Maintain or reduce iron burden in the majority of patients 24 h chelator coverage Control of LPI/NTBI Investigated in large controlled studies and range of diseases
Adverse events	Local, sensorineural, growth, listeria	Agranulocytosis 1.7% weekly CBC monitoring Arthropathy (15%) GI disturbances (33%) Increased ALT	Rash (10%), GI (20%) Increase in creatinine levels (36%) or proteinuria requiring monthly monitoring Increased ALT
Availability	First line agent of transfusional siderosis	Second line agent for TM patients 1999/2004 in Europe when DFO is contraindicated or inadequate 2011 in US, when current chelation therapy is inadequate Limited experience in SCD	FDA 2005: treatment of IO due to TF in pts $\geq$ 2 years EMEA 2006: first line therapy for TM patients $\geq$ 6 years when DFO is contraindicated or inadequate in other anaemias or in patients with TM aged 2–5 yrs
Relative price	++	+	+++

TM: thalassaemia major; TF: blood transfusions; DFO: Deferoxamine; LVEF: left ventricular ejection fraction; NTBI: non-transferrin bound iron; LPI: labile plasma iron.

under DFP therapy) and reducing cardiac mortality in thalassaemia patients. Both controlled and cohort observational studies have shown the cardiac protection of deferiprone. Retrospective Italian analysis clearly reported that patients who switched from DFO to DFP therapy had a lower prevalence of cardiac disease than patients treated with DFO only [30]. In a randomized controlled study comparing the respective effects of DFX and DFO on cardiac iron and function, TM patients with moderate cardiac siderosis experienced a greater improvement under DFP therapy [31]. Recently the same team found that small increases in LVEF in TM patients are associated with a significantly reduced risk of the development of heart failure. Analyzing a large number of patients (315 TM patients) and CMR scans ($n = 754$), 1% absolute increase in LVEF from baseline was associated with a statistically significant reduction in the risk of future development of heart failure [32].

However, deferiprone is associated with a rare, serious, potentially lethal adverse event, agranulocytosis, which limits its use. Neutropenia is more common, reversible with discontinuation of DFP. Weekly blood count monitoring is recommended and immediate medical advice in cases of fever. In the ApoPharma-sponsored clinical trials, agranulocytosis occurred in 1.7%. In Europe, 13 patients (7 TM patients) have died from agranulocytosis during 11 years of post-marketing follow-up. Therefore, the decision to recommend DFP could be partly based on the balance between the risk of a rare and severe adverse event and the cardiac risk of the patient. Limited data are available concerning DFP use in SCD patients.

4.3. Deferasirox (DFX)

Deferasirox is an orally active iron-chelating agent that is given once-daily. Since its approval, mainly based upon the pivotal phase 3 randomized study in thalassaemia patients, important findings and studies have been reported. The effect of DFX was demonstrated to be dose-dependent. Transfusion burden directly influences DFX chelation effectiveness. For example, doses of 20 mg/kg per day produce iron balance in 75% of patients receiving less than 0.3 mg/kg per day of iron versus 50% for patients receiving more than 0.3 mg/kg per day [33]. Tailoring the dose of DFX based on transfusion rate is a safe and effective strategy [34]. Subsequently dose titration every 3–6 months is guided (or is tailored) by trends in SF and safety markers. Doses increased in either 39% of patients (1-year EPIC study), or in 78% (Escalator study). DFX doses up to 40 mg/kg per day are safe and now approved for use in patients inadequately controlled with doses of 30 mg/kg per day [35]. Continuous treatment with high doses of DFX (30–40 mg/kg per day) is able to remove iron from heart in patients with TM. In the cardiac epic sub-study, cardiac T2* improvement over 3 years was demonstrated in 71 patients with initial T2* less than 20 ms [36]. No concomitant improvement in LVEF was noted. DFX therapy may be more effective on cardiac iron in patients with mild to moderate hepatic iron burden [37]. Long-term efficacy and safety of DFX has now been evaluated in both thalassaemia and SCD with few new safety concerns. In thalassaemia, increase in creatinine levels, generally mild or moderate, was observed in 11.2% of the patients, most frequently in patients receiving high doses of DFX. Gastrointestinal (GI side) effects were also more frequent in adults [38]. GI symptoms can lead to discontinuation of the drug. Proximal renal tubular dysfunction has been reported and should be regularly monitored.

The main results of the long-term deferasirox treatment in SCD were high rate of discontinuation (33.5% of completion in the 4-year extension CICL 109 study), and maintenance of normal renal function [28]. Severe renal toxicity rarely occurred and a statistically significant decrease in SF values was observed.

Lack of response to DFX can result from insufficient dosing for high transfusion requirement, poor adherences sometime related to GI side effects but also unfavourable pharmacology. More importantly, the vast majority of patients with hemoglobinopathy live in developing countries where the high cost of DFX remains a concern.

In the French registry the type of iron chelation treatment has changed dramatically over the past six years (Fig. 1A). In 2006, deferoxamine was still the most frequent treatment. It was progressively replaced by deferasirox. DFX is currently the most commonly prescribed chelator being taken in 70% thalassemic patients. The prescription of deferiprone, alone or in combination with deferoxamine

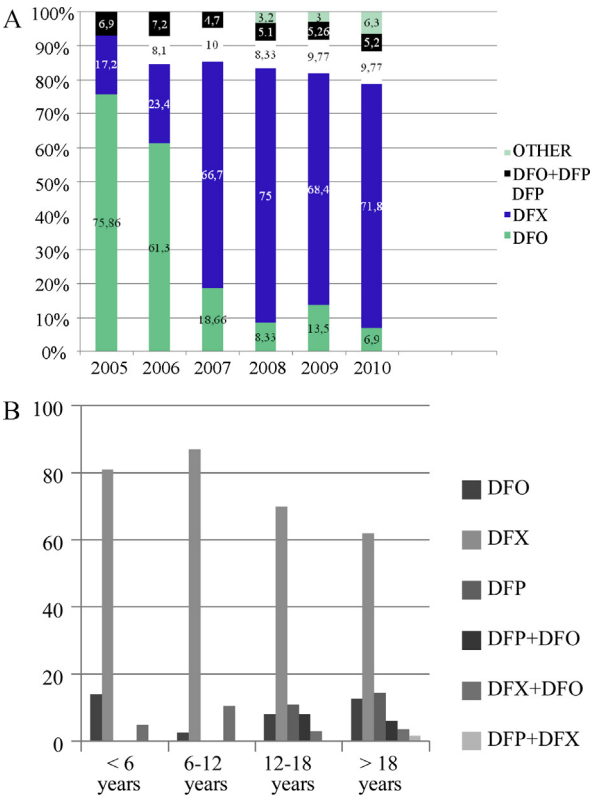

Fig. 1. A and B. French Thalassemia Registry: distribution of chelator agents.

remained stable during the concerned period concerning around 15% of patients. Diversification of chelators use increases with age (Fig. 1B). Of note, during the past 5 years no obvious changes in SF levels distribution were recorded in the registry.

4.4. Combination chelation therapy

4.4.1. Deferiprone and deferoxamine

Combined chelation with DFO and DFP is the most extensively studied combination therapy and has been used off-license since 1998 with an additive or synergistic effect of the two chelators on iron excretion. Combination can be sequential/combined or alternating. Intensive chelation combining DFO and DFP is effective in reducing cardiac siderosis, improving cardiac function and mortality, reversing some endocrine complication [5,39,40]. This combination therapy achieved the most rapid fall in heart and liver iron load compared with DFO monotherapy and is the preferred chelation therapy for many centres for patients with cardiac T2* less than 10 ms or iron related cardiac disease [39], with the aim to produce a potent and continuous treatment.

Intensive chelation combining DFO and DFP can normalize patient's iron load (normal SF, normal cardiac and hepatic MRI findings) with little toxicity and was effective in reversing endocrine complications such as hypogonadism, hypothyroidism in a single uncontrolled adult study [5]. Consequently elevated iron stores (SF > 2500 ng/mL, LIC > 15 mg/gr dw), endocrine complications, in particular abnormal glucose metabolism, usually indicated this combined chelation. Combo is largely prescribed in Cyprus and in Greece particularly to adult patients: introduced in 1999, it was associated with improved survival in the Cyprus beta-thalassaemia registry. Analysis of survival from 1980 to 2004 of 539 patients reported no cardiac death in the group of patients treated with DFP + DFO [41].

Some experiences of other combinations (DFO + DFX, DFX + DFP) were examined in off-label uses, with either synchronous or sequential administration in small case series and pilot studies. Some prospective controlled studies are ongoing in order to determine the efficacy and safety of these two combination treatments.

4.4.2. Deferasirox and deferoxamine

Only pilot studies are currently available. Seven iron overloaded thalassemic patients received within the same week 20 to 30 mg/kg per day of oral deferasirox for four consecutive days, then a subcutaneous infusion of 20 to 40 mg/kg per day of deferoxamine for 8 to 12 hours on the next three consecutive days [42]. The median treatment duration was 25 months (range, 8 to 32). All of the patients showed a decrease in serum ferritin without any side effects. A second preliminary study, using standard doses of both chelators, reported 14 patients treated with deferasirox (7 days/week) and DFO (3 to 7 days/week) [43]. At 6 months, LIC slightly improved with no significant changes in SF and cardiac T2*. Finally, one controlled study combining DFX and DFO for patients with severe cardiac iron overload is ongoing.

4.4.3. Deferasirox and deferiprone

Case-reports have been reported in the literature as well as one non-controlled monocentric study including16 adult thalassemic patients who did not tolerate or refuse DFO [44]. They were treated during 2 years without experiencing unexpected serious adverse event. A significant improvement of SF, cardiac and liver IO was observed as well as amelioration in glucose metabolism. It will be of particular interest to establish in controlled studies, the toxicity profile and the efficacy on cardiac function of the combination of the two oral chelators.

4.5. New chelator agent

A novel oral chelator, a member of the desazadesferrithiocin class of tridentate chelators is under clinical investigation. It is administered once-daily. A 24-week phase 2 study was conducted in 51 adults with transfusional IO [45]. Patients were stratified by iron intake and were randomized to receive two doses. FBS0701 was well tolerated, increased transaminases being the most common treatment related adverse event. The effect of FBS0701 was dose-dependent. Extension study and paediatric phase 2 study are ongoing and both investigate higher doses.

4.6. Compliance

It is well established that compliance is a key factor determining outcome of iron chelation therapy. Patients who comply with DFO therapy have significantly better survival rates than those who do not. The route of administration has an impact on compliance: DFO infusions are time consuming, disrupt daily activities, may be painful and troublesome. Due to the need for 8- to 12-hour infusions, five to seven times per week, compliance with DFO is suboptimal, ranging from 59% to 78%. Oral chelators are easier to use and may improve adherence. Studies of adherence with DFO versus DFP suggest better compliance with DFP [46]. Iron chelation with DFX may be beneficial because it is a once-daily formulation and reduced frequency dosing and fewer numbers of pills generally improve compliance. DFX studies at one year showed that patients were more satisfied with DFX than DFO therapy [47]. Adherence to oral chelators may fall after several years of therapy and when self-reported adherence to iron chelators was studied in the north America Thalassaemia Clinical Research Network, adherence to DFX was only slightly higher than to DFO (97% versus 92%) [48]. In all cases, a multidisciplinary approach taking into account psychological and social aspects is preferred: practical aspects of drug administration should be discussed, adverse events (GI, local) prevented, patients involved in decision making and compliance regularly calculated.

5. Conclusion

The general aim of iron chelation therapy is to efficiently control both cardiac and total body iron burden by maintaining T2* greater than 20ms, LIC less than 7 mg/g liver dw and SF less than 1000 ng/mL. With the recent

advances of iron overload management, iron chelation therapy can be better targeted and individualized according the localization and the degree of iron overload of the patient as well as his tolerance profile.

Improved survival by preventing cardiac death has become a realistic goal of IO therapy thanks to cardiac MRI and the diversification of chelators.

Improved prevention of other morbidities especially endocrine complications including hypogonadism (which was until recently considered as an irreversible complication) could be achieved with a further decrease of global iron load: it has been shown with DFO + DFP combination therapy that near normal iron indices can be reached and that this maximal reduction can reverse endocrine complications in adult patients. In children, the toxicity of DFO (especially on growth) has been associated with the use of high doses and it remains a concern to use hyperchelation in paediatric patients with mild IO. Numerous teams did not stop chelation therapy when SF fall below 500 ng/mL in patients under regular TF but rather decrease the doses of the chelator agent.

Another aspect of chelation therapy, currently investigated by the use of oral chelators, is to further reduce iron toxicity. Continuous chelation therapy theoretically produces a permanent control of plasma NTBI and a permanent prevention of the cellular uptake of NTBI. Labile iron is a key mediator of iron toxicity due to its ability to catalyze production of reactive oxygen species. Thalassemic patients with heart diseases had NTBI levels significantly higher than those without [49]. Levels of antimüllerian hormone (AMH), a sensitive marker for ovarian reserve correlated with non-transferrin-bound iron (NTBI), suggesting a role of labile iron in the pathogenesis of decreased reproductive capacity [50]. Control of labile plasma iron (LPI) is therefore an important aim of chelation therapy. Deferasirox, because of its very prolonged half-life, is a candidate to reach this goal. With deferiprone, drug exposition is less permanent as its half-life is relatively short. Nonetheless its excellent cell penetration, accessibility to intracellular iron pools, ability to redistribute iron within the cell, could improve or prevent iron related cellular damage.

Disclosure of interest

The author declares that she has no conflicts of interest concerning this article.

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