The new era of chelation treatments: effectiveness and safety of 10 different regimens for controlling iron overloading in thalassaemia major

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Summary

This review outlines the effectiveness and safety of 10 different regimens for controlling iron overloading in thalassaemia major (TM). For each treatment, the strength of the evidence was documented according to the guidelines of the American College of Cardiology and the American Heart Association. Serum ferritin (SF), liver iron concentration (LIC), heart T2* signal, heart damage and survival were used to assess effectiveness. Five chelation regimens out of 10 showed Level A Evidence in controlling iron overloading, as determined by SF levels and LIC. Three out of 10 chelation regimens were able to control heart iron levels, as determined by T2* signals with Level A Evidence. Two chelation regimens were able to improve/reverse heart damage and four increased of survival with Level B Evidence. These advances mean that the current survival of TM patients is now similar to that of thalassaemia intermedia patients.

Keywords: thalassaemia, iron overload, chelation.

Iron chelators form complexes with iron to enable its removal from the body in urine or bile. Chelation treatment aims to reduce the labile iron pool or labile intracellular iron within cells, non-transferrin-bound iron outside of cells, and iron overload in the form of ferritin and haemosiderin deposits in different organs. This review addresses the successes and the adverse effects (AEs) of 10 single, alternating or sequential, as well as combined or associated, iron chelation treatments (Table I) in patients with thalassaemia major (TM), updating previous work when only five chelation regimens could be evaluated (Maggio, 2007). The effectiveness of the chelation regimens was assessed according to the principles of evidence-based medicine (EBM) using the levels of evidence designated by the American College of Cardiology (AHA) and the guidelines of the American Heart Association (AHA) (Table II) (Ritchie et al, 1995; Klocke et al, 2003). Table III and Fig 1 report the results of this analysis for each chelation regimen.

Main chelator groups

Chelators can be divided into three main groups according to the way they bind iron: hexadentate (deferoxamine) (DFO), bidentate (deferiprone) (DFP), and tridentate (deferasirox) (DFX) compounds (Table IV). The differences involve changes in molecular weight that lead to differences in intestinal absorption.

Single drug use

Deferoxamine

DFO is a hexadentate iron chelator that binds iron in 1:1 complexes (Table IV). It is infused subcutaneously (s.c.) or intravenously (i.v.); it cannot be orally absorbed (Table IV). DFO has a plasma half-life of 20/30 min, so it does not provide 24-h chelation. However, Pippard et al (1978) showed that reducing the s.c. infusion time to 12 h daily does not appreciably limit the chelating efficiency. The usual daily dose is 20 mg/kg/day for children and 40–60 mg/kg/day for adults (Hershko et al, 1998), and DFO is approved in the US, Canada, Europe and other countries for the treatment of iron overload (Table IV).

Borgna-Pignatti et al (2004) conducted a large observational study involving 977 patients with TM in seven Italian centres and observed a significant association between birth cohort and complication-free survival, as well as a progressively increasing survival rate since 1975 (when DFO was introduced).

The results of a meta-analysis based on nine trials including 400 patients suggested Level A Evidence for DFO regarding the stabilization or ability to decrease body iron burden (Maggio et al, 2011).

DFO can reduce heart iron levels and reverse cardiac complications with improvements in the left ventricular ejection fraction (LVEF) (Davis & Porter, 2000) and progressively
Table I. Possible iron chelation regimens for the treatment of iron overload in thalassaemia major.

<table>
<thead>
<tr>
<th>Type of treatment</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>Deferoxamine</td>
</tr>
<tr>
<td></td>
<td>Deferiprone</td>
</tr>
<tr>
<td></td>
<td>Deferasirox</td>
</tr>
<tr>
<td>Alternating</td>
<td>Deferoxamine and deferiprone</td>
</tr>
<tr>
<td></td>
<td>Deferoxamine and deferasirox</td>
</tr>
<tr>
<td>Combined</td>
<td>Deferoxamine and deferiprone</td>
</tr>
<tr>
<td></td>
<td>Deferoxamine and deferasirox</td>
</tr>
<tr>
<td></td>
<td>Deferiprone and deferasirox</td>
</tr>
</tbody>
</table>

Table II. Levels of evidence for individual class assignments according to the American College of Cardiology and the American Heart Association (Ritchie et al., 1995; Klocke et al., 2003).

<table>
<thead>
<tr>
<th>Level</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Data derived from multiple randomised clinical trials</td>
</tr>
<tr>
<td>B</td>
<td>Data derived from a single randomised trial, or from non randomised studies</td>
</tr>
<tr>
<td>C</td>
<td>Consensus opinion of experts</td>
</tr>
</tbody>
</table>

increase myocardial T2* signals (Anderson et al., 2004). However, more recent randomized clinical trials have suggested that the LVEF at the end of the intervention was significantly increased in the DFP plus DFO groups, which were administered in combination either simultaneously [weighted mean difference (WMD) 3.37, 95% confidence interval (CI) 0.79–5.95, \( P = 0.01 \)] or sequentially [WMD 9.02, 95% CI 6.4–11.64, \( P = 0.00001 \)] (Abdelrazik, 2007; Aydinok et al., 2007; Tanner et al., 2007; Maggio et al., 2011).

The following AEs have been extensively described: local skin reactions, hypersensitivity, impaired skeletal development, infection with Yersinia enterocolitica, ophthalmic toxicity and ototoxicity, renal impairment and pulmonary fibrosis (Bousquet et al., 1983; Olivieri et al., 1986; De Virgilis et al., 1988; Koren et al., 1991; Rodda et al., 1995). These AEs are generally considered to be dose-related, and anaphylaxis is rare.

Conclusions. These findings provide Level A Evidence regarding the effects of DFO on serum ferritin (SF) and liver iron concentration (LIC) and Level B Evidence for heart T2* signals, heart damage and survival.

Deferiprone

DFP is a bidentate iron chelator that binds iron in 3:1 complexes (Table IV), and it was the first orally active iron-chelating drug to be developed (Kontoghiorghes, 1982). It is administered at a dosage of 75–100 mg/kg/day divided over three administrations (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000236/human_med_000789.jsp&mid=WCOB01ac058001d124), and it has been approved in Europe, India and other countries for use when DFO therapy is contraindicated (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000236/human_med_000789.jsp&mid=WCOB01ac058001d124) and in the US since October 2011 for use when chelation therapy with DFX or DFO is inadequate (Traynor, 2011) (Table IV).

The efficacy of DFP has largely been proven. The results of a 1-year randomized, controlled trial involving 144 patients suggested that DFP (75 mg/kg/day) is as effective as DFO for the treatment of iron overload in TM patients (Maggio et al., 2002). Moreover, Maggio et al. (2011) conducted a meta-analysis of four different randomized clinical trials involving 1520 patients with TM, and this analysis did not show any differences in SF between the two groups after 12 months of treatment.

Viprakasit et al. (2013) conducted a study of 73 paediatric patients with TM (age range, 3–219 years) and found that DFP at a dose of 79.1 ± 4.3 mg/kg/day changed SF from baseline in 45% of patients with a median reduction of 1065 µg/l. Furthermore, doses of 100 mg/kg/day were shown to be safe and efficacious in decreasing SF over a 2-year period in 12 TM patients (Taher et al., 2005).

The most important AEs are neutropenia and agranulocytosis, with incidences of 2.1 to 5.4/100 patient-years and 0.4 to 0.6/100 patient-years, respectively (Cohen et al., 2000; Ceci et al., 2002). Therefore, constant monitoring of white blood cell counts is required. The causes of neutropenia and agranulocytosis are unknown, and other AEs include gastrointestinal (GI) symptoms, hypertransaminasaemia (Taher et al., 1997; Maggio et al., 2002), arthropathy, arthralgia (Cohen et al., 2000; Maggio et al., 2002) and occasional zinc deficiency (Hoffbrand et al., 1998).

Regarding the natural history of TM, randomized and retrospective clinical trials have suggested that DFO treatment is associated with a significant increase in cardiac protection against iron overloading compared with DFO (Borgna-Pignatti et al., 2006; Galanello et al., 2006a; Pennell et al., 2006; Smith et al., 2011; Maggio et al., 2012; Filosa et al., 2013; Kuo & Mrkobrada, 2014).

Borgna-Pignatti et al. (2006) compared the occurrence of cardiac disease in patients treated only with DFO with those whose treatment was switched to DFP. Overall 3610 and 750 patients were observed on DFO and DFP, respectively. Fifty-four cardiac events, including 10 cardiac deaths, occurred during therapy with DFO and no cardiac events occurred during DFP treatment or within at least 18 months after treatment ended.

In a randomized controlled trial, Pennell et al. (2006) showed that the improvement in myocardial T2* was significantly greater for DFP compared with DFO (27% vs. 13%; \( P = 0.023 \)). Moreover, there was a significant increase in
Table III. Levels of evidence for effectiveness according to different outcomes for the 10 different iron chelation regimens in thalassaemia major. The levels of evidence were based on American College of Cardiology and the American Heart Association guidelines (Ritchie et al, 1995; Klocke et al, 2003).

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Serum ferritin</th>
<th>LIC (†)</th>
<th>Heart T2*</th>
<th>Heart damage (‡)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (RCT)</td>
<td>Number (NRCT)</td>
<td>Number (CoE)</td>
<td>Number (Pts)</td>
<td>Number (LoE)</td>
</tr>
<tr>
<td>DFO</td>
<td>9</td>
<td>400 A</td>
<td>9</td>
<td>400 A</td>
<td>1</td>
</tr>
<tr>
<td>DFP</td>
<td>3</td>
<td>1</td>
<td>388 A</td>
<td>388 A</td>
<td>2</td>
</tr>
<tr>
<td>DFX</td>
<td>5</td>
<td>3</td>
<td>1274 A</td>
<td>1154 A</td>
<td>2</td>
</tr>
<tr>
<td>DFX twice daily Alternating DFO and DFP</td>
<td>2</td>
<td>2</td>
<td>25 C</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Alternating DFO and DFP</td>
<td>1</td>
<td>7</td>
<td>C</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Combined DFO and DFP</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2 C</td>
</tr>
<tr>
<td>Combined DFO and DFP</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>244 A</td>
</tr>
<tr>
<td>Combined DFO and DFP</td>
<td>4</td>
<td>2</td>
<td>131 B</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Combined DFO and DFX</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>163 B</td>
<td>1</td>
</tr>
</tbody>
</table>

NA, not available; (†), liver iron concentration (LIC) determined by T2* or Liver Biopsy; (‡), heart damage if ejection fraction <50% or proven cardiac disease; RCT, randomised clinical trial; NRCT, none randomised clinical trial; CoE, consensus opinion of expert; Pts, patients (this number includes subjects in the experimental and control arms); LoE, level of evidence according to Ritchie et al (1995) and Klocke et al (2003); DFO, deferoxamine; DFP, deferiprone; DFX, deferasirox.

*Maggio et al (2009a), although in this study 275 patients were randomised, only 54 patients underwent T2* heart signal determination.
LVEF in the DFP-treated group (3-1% vs. 0-3% absolute units; \( P = 0.003 \)). Galanello et al (2006a) suggested that DFP alone seems to be superior to DFO monotherapy in improving myocardial siderosis and cardiac function. Smith et al (2011) re-analysed the right ventricular volume (RVESV) data reported by Pennell et al (2006) and showed that monotherapy with DFP decreased RVESV and increased the right ventricular ejection fraction (RVEF) compared with DFO. Maggio et al (2012) and Filosa et al (2013) showed that long-term treatment with DFP alone significantly improved LVEF compared with DFO alone and sequential DFP-DFO chelation treatment, and this observation may explain the survival data reported by Borgna-Pignatti et al (2006).

In a systematic review and meta-analysis comparing DFP and DFO, Kuo and Mrkobrada (2014) found that DFP was more efficacious than DFO in improving LVEF [mean difference (MD) 2.88, 95% CI 1.12–4.64, \( P = 0.001 \)] and endocrine dysfunction (MD 0.09, 95% CI 0.08–0.10, \( P < 0.0001 \)). These findings could be explained by the ability of DFP to preserve cardiac contractility by protecting mitochondrial function and structure from damage induced by oxidative stress (Link et al, 1999; Xu et al, 2006).

Conclusions. These findings provide Level A Evidence regarding the effects on SF, LIC and heart T2* and Level B Evidence for survival. No data regarding the ability of DFP alone to reverse heart damage are currently available.

Deferasirox

DFX is a tridentate iron chelator that binds iron in 2:1 complexes (Table IV). It is recommended for patients with iron overload, defined as a cumulative transfusion of 100 ml/kg of packed red blood cells and a SF consistently >1000 \( \mu \)g/l. The highest approved dose of DFX is currently 30 mg/kg once or twice daily in many countries. However, some patients require escalation to 20–40 mg/kg/day to achieve the therapeutic goal. Galanello et al (2006b) showed that DFX was well tolerated by the paediatric population (2 years or older) and, in a randomized phase II trial, Piga et al (2006) showed that DFX administered at daily doses of 10 or 20 mg/kg was well tolerated. Moreover, a dose of 20 mg/kg had similar efficacy to 40 mg/kg of DFO in terms of decreasing LIC. Cappellini et al (2006) conducted a trial involving 586 patients with TM, with 296 and 290 patients receiving DFX and DFO, respectively. The primary response criterion was defined as the maintenance or reduction of LIC measured by liver biopsy or superconducting quantum interference device. Although well tolerated, the 10 mg/kg/day dosage of DFX did not induce a negative iron balance because it was considered too low. Patients with a LIC >7 mg Fe/g dry weight (dw) exhibited a significant and similar dose-dependent reduction in LIC and SF compared with patients in DFO group. The results of the trial suggested that DFX dosages of 30 mg/kg/day induced a negative iron balance with a significant decrease in LIC. The ESCALATOR study, whose primary endpoint was a reduction in LIC, included 233/237 enrolled patients who completed 1 year of treatment and found that DFX had a significant treatment success rate of 57.0% \( (P = 0.016) \) and resulted in a mean LIC reduction of 3.4 mg Fe/g dw (Taher et al, 2009a). Most patients (78-1%) underwent dosage increases from 20 to 30 mg/kg/day (Taher et al, 2009a). In a retrospective analysis of 264 patients who received dosages of >30 mg/kg/day with a median exposure of 36 weeks, Taher et al (2009b) observed a statistically significant decrease in the median SF of 440 \( \mu \)g/l \( (P < 0.0001) \). Furthermore, Chang et al (2015) found that after 7 years of treatment with DEX, the mean SF decreased significantly by 2566 \( \mu \)g/l \( (P < 0.001) \) and, in a 5-year study, Casisnerio et al (2015) observed a significant reduction in LIC (5.36 ± 3.58 mg/g dw at baseline versus 3.35 ± 2.68 mg/g dw at final evaluation, \( P = 0.004 \)).
Table IV. Comparison of chelator properties in preclinical studies and their clinical stage of development.

<table>
<thead>
<tr>
<th>Group</th>
<th>Compound</th>
<th>Route of administration</th>
<th>Studies</th>
<th>Clinical stage</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexadentate (1:1)</td>
<td>Deferioxamine</td>
<td>Subcutaneous, intravenous</td>
<td>Phase I/II/III</td>
<td>Marketed in US, Canada and Europe (1968)</td>
<td>Novartis (Basel, Switzerland)</td>
</tr>
</tbody>
</table>

Table V. Deferiprone (DFP) and deferoxamine (DFO) combined chelation treatment: published schedules of administration.

<table>
<thead>
<tr>
<th>Study</th>
<th>Dosage of DFP (mg/kg/day)</th>
<th>Dosage of DFO (mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mourad et al (2003)</td>
<td>75</td>
<td>50 (2 days/week)</td>
</tr>
<tr>
<td>Gomber et al (2004)</td>
<td>75</td>
<td>40 (2 days/week)</td>
</tr>
<tr>
<td>Aydinok et al (2007)</td>
<td>75</td>
<td>40–50 (2 days/week)</td>
</tr>
<tr>
<td>Ha et al (2006)</td>
<td>75</td>
<td>30–60 (2 days/week)</td>
</tr>
<tr>
<td>Abddebraiik (2007)</td>
<td>75</td>
<td>40 (2 days/week)</td>
</tr>
<tr>
<td>Tanner et al (2007)</td>
<td>75</td>
<td>30–50 (5 days/week)</td>
</tr>
<tr>
<td>Tamaddoni and Ramezani (2010)</td>
<td>75</td>
<td>40–50 (2 days/week)</td>
</tr>
</tbody>
</table>

Recently, a prospective, randomized study involving 60 patients with TM over a period from September 2014 to September 2015 did not show any significant differences in SF (P = 0.673) or per cent reduction in ferritin (P = 0.315) between the DFX and DFO groups (Hassan & Tolba, 2016).

The EPIC cardiac sub-study revealed a significant reduction in cardiac iron levels (P < 0.001) assessed by heart T2* over 3 years of treatment in patients with TM (Pennell et al, 2012).

CORDELIA, a prospective, randomized comparison study of DFX (a target dosage of 40 mg/kg/day) versus s.c. DFO (50–60 mg/kg/day for 5–7 weeks) that evaluated myocardial iron removal in 197 TM patients with myocardial siderosis (T2*, 6–20 ms) and no signs of cardiac dysfunction (mean age, 19.8 years) demonstrated the non-inferiority of DFX compared with DFO for myocardial iron removal (Pennell et al, 2014). Furthermore, Chang et al (2015) and Vlachaki et al (2015) confirmed the effectiveness of DFX for myocardial iron control after 7 and 5 years of chelation treatment.

However, although the non-inferiority of DFX compared with DFO for myocardial iron removal has been demonstrated, the LVEF remained stable during treatment with DFX (Baksi & Pennell, 2014). Therefore, the AHA guidelines do not recommend the use of DFX as a first-line treatment when there is established depression of LVEF or for those with severe iron loading (Carpenter et al, 2013).

One-third of patients find the formulation of DFX as a tablet for oral suspension to be unpalatable (Chalmers & Shammo, 2016). Therefore, a new tablet formulation has been developed in an attempt to overcome these tolerability issues, and was approved by the US Food and Drug Administration (FDA) on 31 March 2015 (Table IV). These DFX tablets contain the same active ingredient as DFX tablets for oral suspension, but the peak serum concentrations (Cmax) is approximately 30% higher. The new formulation is also 36% more bioavailable than the original formulation. Therefore, when converting a patient from DFX tablets for oral suspension (Exjade®) to DFX tablets (Jadenu®), the dosage should be decreased by 30%; treatment with DFX tablets should be initiated at 14 mg/kg/day and titrated up by 3.5–7 mg/kg/day (Chalmers & Shammo, 2016) with a maximum dosage of 28 mg/kg/day. A phase 2 randomized, open-label, multicentre, two-arm study comparing the safety of the two formulations is ongoing (NCT02125877).

The most common AEs of DFX are GI events, which are observed in 10–33% of cases and include abdominal pain, diarrhoea, nausea and/or vomiting, and result in the termination of drug treatment in 7% of cases (Chalmers & Shammo, 2016). As the new formulation lacks lactose and sodium sulphate, which are potentially implicated in the GI AEs, it is hypothesized that this could improve tolerability (Nolte et al, 2015). However, confirmation of this hypothesis is pending until the results of the prospective trial comparing the two formulations of DFX are available. GI haemorrhage and thrombocytopenia have also been reported in patients with advanced haematological malignancies (Gattermann & Rachmilewitz, 2011), and DFX is contraindicated in patients with platelet counts <50 × 10^9/l (Gattermann & Rachmilewitz, 2011). As DFX can cause renal toxicity and proteinuria, creatinine levels should be measured twice prior to the initiation of therapy and monthly thereafter (Dee et al, 2014). For patients with creatinine clearance of 40–60 ml/min, the starting dose should be reduced by 50% (Chalmers & Shammo, 2016), and its use is not advised for patients with creatinine clearance <40 ml/min. If a patient develops an elevation in creatinine during treatment that is >33% of baseline and
sustained for 1 week, the dose should be decreased by 7 mg/kg/day for DFX tablets (Chalmers & Shammo, 2016). The medication should be withheld if the creatinine clearance is <40 ml/min, and the dose adjustment for liver disease depends on the degree of liver dysfunction. Similar to DFO, neurosensory deafness and hypoacusia have been reported, and bile acid sequestrates and uridine 5'-diphospho-glucuronyltransferase inducers, such as phenytoin or ritonavir, have the potential to lower the concentration of DFX. Aluminium-containing antacid preparations should not be administered with DFX, and drugs metabolized by CYP3A4 may be made less effective by DFX. Additionally, due to the known risk of GI haemorrhage, medications that can cause ulcers or those with a haemorrhagic potential should be avoided (Chalmers & Shammo, 2016).

Finally, the efficacy of DFX administered twice daily has also been proven. Pongtanakul and Viprakasit (2013) have shown that twice-daily dosing of DFX significantly improves clinical efficacy in patients with TM who had inadequate responses to the standard once-daily dose, with a significant decrease in SF. Recently, pharmacokinetic studies of DFX comparing once-daily and twice-daily administration found that twice-daily administration of DFX increased the mean trough levels of DFX [183-8 (157-5) μmol/l] compared with once-daily administration [87-7 (56-8) μmol/l] (Lu et al, 2015). However, more extensive trials are necessary to confirm these results.

Conclusions. These findings provide Level A Evidence regarding the effects of once-daily administration of DFX on SF, LIC and heart T2*. To date, no data are available regarding the effects of once-daily DFX administration on the reversal of heart damage and improvement of survival. Level C Evidence was observed for the effects of twice-daily administration of DFX on SF.

Alternating or sequential regimens

Deferoxamine and deferasiprone

Treatment with DFO and DFP was introduced to manage iron overload in patients who were suboptimally chelated with maximum doses of DFP (Wonke et al, 1998). The synergistic effects of DFP and DFO on iron balance and urine iron excretion have been explained by a shuttle mechanism, and two administration routes have been used for this chelation treatment. The first regimen, in which DFO and DFP are administered on the same day, is referred to as combined or associated treatment. The second, in which DFO is administered on different days than DFP, is referred to as alternating or sequential treatment. The latter treatment should decrease the AEs of these chelators and improve compliance, and this regimen will be addressed in this section.

Galanello et al (2006a) compared the efficacy and safety of alternating DFO and DFP with that of DFO alone. Sixty TM patients regularly treated with DFO were randomized to a group that continued to receive DFO alone or to a group that received alternating treatment for 1 year. The first group continued to receive DFO at the same dose for 5–7 days/week for 12 months, and the second group received alternating regimens of 75 mg/kg/day of DFP divided into three daily oral doses 5 days/week and DFO the other 2 days of the week. Both arms exhibited equivalent decreases in SF (−228 ± 791 μg/l) for the alternating therapy group versus −349 ± 573 μg/l for the DFO alone group; \( P = 0.5802 \) and LIC (−65 ± 615 vs. −239 ± 474 μg Fe/g dw, \( P = 0.2263 \)), and there was no significant difference in the proportion of patients with adverse events between the two treatment groups, although their nature differed according to the chelation regimen. Abdelrazik (2007) showed that alternating DFP (75 mg/kg/day for 4 days/week) and DFO (40 mg/kg/day for 2 days/week) resulted in significant improvement in SF and urine iron excretion compared with DFO alone. In a multicentre, randomized, open-label trial involving 275 TM patients, Maggio et al (2009a), assessed the effectiveness of long-term sequential DFP-DFO treatment versus DFP alone. DFP at a dose of 75 mg/kg divided into three oral daily doses for 4 days/week and DFO administered by s.c. infusion (8–12 h) at 50 mg/kg/day for the remaining 3 days/week was compared with DFP alone at a dose of 75 mg/kg administered 7 days/week during a 5-year follow-up, and the magnitude of the decrease in SF during the treatment period was greater in the sequential DFP-DFO patients compared with the DFP-alone patients (\( P = 0.005 \)). Maggio et al (2009a) found that the long-term use of sequential DFO-DFP increased LVEF, although the variation over time was inferior to the DFP-alone group (Maggio et al, 2012). A Kaplan–Meier survival analysis of the two treatments did not reveal any statistically significant differences (log-rank test, \( P = 0.3145 \)), and the amount of adverse events and costs were comparable between the two groups.

Conclusions. These findings provide Level A Evidence for the effects on SF and LIC, and Level B Evidence for heart T2* and survival. The data regarding the effects of this regimen on heart damage are not yet available.

Deferoxamine and deferasirox

Only one report has retrospectively addressed alternating or sequential means of DFO and DFX administration (Jetsirisaparb et al, 2010). In this paper, 7 iron-overloaded thalassemic patients who experienced problems when treated with iron chelators received 20–30 mg/kg/day of DFX for 4 consecutive days followed by s.c. infusion of 20–40 mg/kg/day of DFO for 8–12 h on the next 3 consecutive days. The median treatment duration was 25 months (range, 8–32), and all of the patients exhibited a decrease in SF without any AEs. However, prospective or randomized clinical trials are
needed to evaluate the safety and efficacy of this type of treatment.

Conclusions. These findings provide Level C Evidence for the effects on SF. No data are currently available regarding LIC, heart T2*, heart damage and survival.

Deferoxamine and deferasirox

Further studies are needed to confirm the effectiveness and safety of alternating DFP and DFX. Indeed, Balocco et al (2010) reported only two cases of patients who were effectively treated with this method of alternating chelation. However, a multicentre, randomized clinical trial with 63 patients comparing alternating DFX–DFP to either DFX or DFP is ongoing (Vitrano et al, AOR Villa Sofia-V. Cervello, Palermo, Italy, personal communication).

Conclusions. These findings provide only Level C Evidence for the effects on SF, LIC and heart T2*. No other data are available for heart damage and survival.

Combined or associated regimens

Deferoxamine and deferiprone

The first study to show the success of combined treatment with DFO and DFP in five patients with TM was reported by Wonke et al (1998). Subsequently, larger prospective and randomized clinical trials addressed this issue in detail.

Table V shows the various published dosage schedules and frequencies per week for DFP and DFO administration that have been reported to date. These variations could explain some of the differences observed among various protocols in terms of changes in SF and heart T2* values at the end of treatment. Moreover, the doses referred to in Table V are not necessarily those that are now used in clinical practice, suggesting great heterogeneity in the scheduling of dosages and frequency per week of administration of DFP and DFO in this kind of chelation regimen.

According to Galanello et al (2010), extensive long-term experience has shown that chelation with combined DFP and DFO rapidly reduces LIC, SF and myocardial siderosis. Moreover, it improves cardiac function, reverses and prevents endocrine complications, reduces cardiac mortality and improves survival.

Maggio et al (2011) reviewed the effectiveness and safety of this type of treatment in a systematic meta-analysis review that included all of the papers presented in Table V. The outcomes considered to be indicative of the effectiveness of treatment were LIC (mean change from baseline), SF at the end of the intervention, and the change in SF from baseline to the end of the intervention. The results suggested that the combination treatment had a statistically significant advantage over DFO treatment alone in terms of decreasing LIC and SF.

The ability of combined treatment to reverse cardiac dysfunction and increase LVEF function in TM patients has been clearly demonstrated. In a randomized clinical trial involving 65 patients that compared DFO plus DFP to standard monotherapy with DFO, Tanner et al (2007) found that DFO plus DFP was able to improve myocardial T2* (ratio of change in geometric means, 1.50 vs. 1.24, P = 0.02), absolute LVEF (2.6% vs. 0.6%, P = 0.05), and absolute endothelial function (8.8% vs. 3.3%, P = 0.02).

In a study of 65 TM patients with mild-moderate cardiac siderosis receiving either combination therapy or DFO, Alpendurada et al (2012), re-analysing the data of two previous trials (Tanner et al, 2007, 2008) for RVEF responses, found that DFO plus DFP was superior to DFO alone for improving RVEF (3.6% vs. 0.7%, P = 0.02). The increase in RVEF was greater with a lower baseline T2* of 8–12 ms (4.7% vs. 0.5%, P = 0.01) than with a T2* of 12–20 ms (2.2% vs. 0.8%, P = 0.47).

Tanner et al (2008) reported the effects of combined chelation treatment given to 15 patients with severe myocardial siderosis (T2* < 8 ms) for 12 months. The myocardial T2* improved (from 5.7 ± 0.98 to 7.9 ± 2.47 ms; P = 0.010), with concomitant improvement in LV ejection fraction (from 51.2 ± 10.9% to 65.6 ± 6.7%; P < 0.001).

Pepe et al (2013) compared 51, 39 and 74 patients who were treated in routine clinical practice with DFO, DFP, and DFO plus DFP, respectively, and found that the DFP plus DFO regimen was more effective in removing cardiac iron than DFO. Moreover, the combination DFP plus DFO chelation was better able to clear hepatic iron than either DFO or DFP monotherapy. However, no additional effects on heart function were observed compared with DFP alone (Pepe et al, 2013).

Kuo and Mrkobrada (2014) conducted a meta-analysis and found that therapy with DFP plus DFO was more efficacious than monotherapy with either DFP or DFO in improving LVEF (MD 5.67, 95% CI 1.32–10.02, P = 0.008).

Tefer et al (2009) reported increased survival in TM patients after switching from DFO to combined chelation therapy. Furthermore, no deaths occurred with either DFP alone or DFP plus DFO during a multicentre, long-term, randomized controlled trial (Maggio et al, 2009b).

Lai et al (2010) conducted a prospective study of 28 patients with TM and cardiac disease that lasted 42 ± 6 months in which 15 patients were given DFP plus DFO (DFP, 75 mg/kg t.i.d.; DFO, 40–50 mg/kg over 8–12 h at night 5–7 days/week), while 13 patients (five with high and eight with low ferritin levels) received DFO alone. No cardiac events were observed among the high-ferritin patients receiving combination therapy, whereas four cardiac events (P = 0.0049), including three deaths, occurred in the high-ferritin patients receiving DFO monotherapy.
Based on these findings, the European Medical Agency suggested on 28 April 2016 that the summary of product characteristics (SmPC) for DFP in combination with another chelator be updated (http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/000236/WC500205478.pdf). The updated SmPC recommendations state that the addition of DFP is indicated for patients with TM when monotherapy with any iron chelator is ineffective or when the prevention or treatment of life-threatening consequences of iron overload (mainly cardiac overload) justifies rapid or intensive intervention.

Conclusions. These findings provide Level A Evidence for the effects on SF, LIC and heart T2* and Level B Evidence for the effects on heart damage and survival.

Deferoxamine and deferasirox

The daily use of DFX with 2–3 days of DFO treatment has been shown to place patients into net negative iron balance (Grady et al, 2013).

Lal et al (2013) conducted a trial examining the effects of DFX (20–30 mg/kg/day) plus DFO (35–50 mg/kg, 3–7 days/week) in 22 patients with persistent iron overloading. Eighteen of these patients completed 12 months of treatment, and the median LIC decreased by 31%, from 17.4 mg/g (range 3.9–38.2 mg/g) to 12.0 mg/g (range 0.96–26.7 mg/g, P < 0.001). The median SF decreased by 24%, from 2465 µg/l (range 1110–10 700 µg/l) to 1875 µg/l (range 421–5800 µg/l, P = 0.002), and all six of the subjects with elevated myocardial iron levels showed improvement in heart T2* (P = 0.031).

Voskaridou et al (2014) reported a case involving a 40-year-old male with TM and severe liver and cardiac iron overload. Eighteen months of treatment with DFX (30 mg/kg/day/7 days/week) plus DFO (50 mg/kg/day/4 days/week) had beneficial effects on heart and liver haemosiderosis, while no adverse events were reported.

In a study of 20 TM patients who were treated for 1 year with DFO (32 ± 4 mg/kg/day, 3–4 days/week) plus DFX (20 ± 2 mg/kg/day), Cassiniero et al (2014) observed a marked reduction in LIC (6.54 vs. 11.44 mg/g dw at baseline) and in the median SF (1346 vs. 2254 µg/l at baseline). However, an improvement in cardiac T2* values (26.34 ± 15.85 vs. 19.85 ± 12.06 at baseline) was reported.

Arandi et al (2015) observed a significant reduction in SF (from 4031 ± 1955 to 2416 ± 1653 µg/l) and an improvement of echocardiographic findings (P ≤ 0.001) after 12 months of combined treatment with DFX (30–40 mg/kg/day) and DFO (40–50 mg/kg/day, 2 days/week). No drug toxicity was observed based on the monitoring of serum creatinine, liver enzymes and blood urea nitrogen.

The HYPERION study, which was an open-label single-arm prospective phase 2 study of TM patients with severe transfusional myocardial siderosis (heart T2* 5 < 10 ms) and an LVEF ≥56%, evaluated the effects of the combination of DFX plus DFO followed by an optional switch to DFX alone when achieving a heart T2* >10 ms. The mean dosages were 30–5 and 36–3 mg/kg/day on a 5-day regimen for DFX and DFO, respectively. The findings showed meaningful improvements in heart T2* in about one-third of the patients remaining on treatment at month 24. The LIC decreased substantially, from a baseline of 33.4–12.8 mg Fe/g dw at month 24 (–52%), and LVEF remained stable with no new arrhythmias and/or cardiac failure. The safety was consistent with established monotherapies (Aydinok et al, 2015).

Conclusions. These findings provide Level B Evidence for the effects on SF, LIC and heart T2*. No data are yet available regarding heart damage and survival.

Deferiprone and deferasirox

Several ongoing and completed studies have demonstrated the efficacy and safety of chelation combined with DFP plus DFX.

Voskaridou et al (2011) reported successful chelation treatment with DFP (75 mg/kg/day) plus DFX (30 mg/kg/day) in a 34-year-old patient with TM and persisting severe iron overload after single-agent chelation therapies. In the same year, Farmaki et al (2011) published data involving 16 patients who were treated with DFP (75–100 mg/kg/day) plus DFX (20–25 mg/kg/day), and improvements in LVEF, gonadal function and glucose metabolism were reported.

Alavi et al (2014) described the success of combined treatment with DFP (75 mg/kg/day in 3 doses/day) plus DFX (25 mg/kg/day) in a 25-year-old TM patient, reporting both SF reduction and normalization of liver and cardiac MRI indices.

Elalfy et al (2015) reported the results of a large prospective, randomized clinical trial involving 96 young TM patients with severe iron overload. These patients were randomized in groups that received either DFP with DFO or DFP plus DFX, and the SF and LIC at 12 months were significantly reduced in both arms. The geometric mean of the cardiac T2* values was higher compared with baseline, and significant differences were observed between the rates of change of the two groups (P = 0.001). Treatment with DFP plus DFX resulted in more improvement, and the safety report did not indicate any serious AEs necessitating discontinuation or interruption of treatment for both groups. No cases of agranulocytosis were reported, but neutropenia, arthralgia, GI problems, increases in alanine transaminase (>3-fold) and serum creatinine (>33%) were described in both arms of the study. However, skin rashes were only observed in the DFP plus DFX group.

Gomber et al (2016) compared treatment with DFP plus DFX to monotherapies in 49 multi-transfused children with TM. After 12 months of treatment, the SF values decreased from a mean of 3140.5–2910.0 µg/l in the DFP alone group,
3859.2–3417.4 µg/l in the DFX alone group and 3696.5–2572.1 µg/l in the DFP plus DFX group. The combination therapy was more efficacious in decreasing the SF than monotherapy with DFP or DFX (P = 0.035 and 0.040, respectively).

Conclusions. These findings provide Level B Evidence for the effects on SF, LIC and heart T2*. No data are yet available regarding heart damage and survival.

Initiating chelation treatment

Recently, Danjou et al (2014) suggested that chelation therapy should be initiated when more than 1000 g of RBCs have been transfused or when transferrin saturation is over 90% in patients with less than 1000 g of RBCs transfused.

The treatment should also be initiated when SF is >1000 µg/l or LIC >7 mg Fe/g dw.

The most current guidelines (Saliba et al, 2015) suggest DFO at a dose of 20–40 mg/kg/day 5–7 times per week as the recommended chelator for first-line treatment of children between the ages of 2 and 6 years in Europe, the UK and Canada, while DFX at 20–40 mg/kg/day may be used as a first-line treatment in the US and Australia. Finally, the evaluation of DFP in the paediatric population is ongoing thanks to the DEEP European Grant Project (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicine/s/000236/human_med_000789.jsp&mId=WCOb01ac0580001d124), and Bellanti et al (2016) suggest that the same dosages of DFP that are used in adults may be used in these cohorts.

Pregnancy and chelation

DFO must be used with caution during pregnancy (Bosque et al, 1995). However, the majority of women who are treated with DFO during the second and third trimesters have normal pregnancy outcomes (McElhatton et al, 1991). The risk of spontaneous abortion is low, but it cannot be excluded (McElhatton et al, 1991). Hence, DFO has been assigned to pregnancy category C by the FDA.

DFP treatment has not been adequately studied (Shilalukey et al, 1997), and no carcinogenetic studies have been conducted in animals. Based on the above, DFP has been assigned to pregnancy category D by the FDA. Women of childbearing age treated with DFP must be advised to avoid pregnancy due to the clastogenic and teratogenic properties of DFP.

DFX has also been assigned to pregnancy category C by the FDA, as animal studies have revealed evidence of embryo fetotoxicity. These studies showed decreased offspring viability and increased renal anomalies (Anastasi et al, 2011; Vini et al, 2011; Diamantidis et al, 2016).

Conclusions. Iron chelation therapy is not generally recommended during pregnancy and/or for breastfeeding women. Additionally, DFO, DFP and DFX should only be used during pregnancy if the potential benefits outweigh the potential risk to the fetus.

Compliance

The survival of TM patients has improved to levels that are comparable to thalassaemia intermedia (TI) patients (Vitrano et al, 2017). However, heart damage still remains the major cause of death (Vitrano et al, 2017), and this scenario can only be explained by ‘compliance failure’.

Non-compliant patients do not follow the recommendations of clinicians. Therefore, the patient’s behaviour results in treatments that are ineffective, regardless of the type of treatment, even including monotherapy. This may be explained because humans often do not act consistently or obey the laws of rational choice theory (Cowdry, 2008). Therefore, to be effective, each intervention aimed at changing behaviour must take into account the emotional sphere of the patient.

Different approaches, even randomized clinical trials involving behaviour change interventions, have been developed for other chronic diseases, such as diabetes and tuberculosis, but not for TM (Lustman et al, 1998; Katon et al, 2004; Peyrot & Rubin, 2007; Lutge et al, 2015). Self-enforcement, contracting for change and emotional support have been the basis of these interventions (Carver & Scheier, 1998; Rubin & Peyrot, 2001; Peyrot & Rubin, 2007).

Conclusions. Prospective and/or randomized clinical trials aimed at changing behaviour to improve chelation ‘compliance’ are strongly recommended.

Areas of uncertainty and future strategies

The impact of different treatment schedules, especially for regimens involving a combination of DFO plus DFP and whether the combination of DFO and DFX or DFP is a better treatment strategy, are the two main areas of uncertainty.

Therefore, randomized clinical trials with more neglected regimens such as DFX twice daily, alternating DFO and DFX and alternating DFP and DFX protocols should be conducted in the future (Table III, Fig 1). This goal can only be reached if academic, national health and European community institutions, as well as international non-profit organizations, decide to invest in this field. Moreover, a deeper analysis of the organ specificity of these regimens will further aid in the prevention of complications, and randomized clinical trials aimed at changing behaviour to increase ‘compliance’ may be another possible strategy.

Conclusions

Chelation therapy has advanced since 1962 when DFO was first shown to be effective. By 2006, 10 different chelation
treatments had been identified, which initiated a new era of chelation (Table III). In terms of effectiveness and safety, these advances are very impressive, and combined with the improved safety of red cell transfusions, mean that survival in TM is now similar to that in TI (Vitrano et al., 2017). This may indicate a need to review approaches to the management of patients in the latter group.

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Author contributions

Both authors performed data collection, assembly and critical revision of the manuscript for intellectual content, and approved the manuscript prior to submission.

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